DOI: 10.1002/adsc.200600361

Enantioselective Carbonyl-Ene Reactions of Arylglyoxals with a Chiral Palladium(II)-BINAP Catalyst

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Received: July 18, 2006; Revised: March 30, 2007

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The palladium(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions between ten arylglyoxals and five alkenes were systematically investigated and demonstrated good to excellent enantioselectivities with high *ee* values of up to 93.8%. The results showed that both arylglyoxals and alkenes exert evident effects on the enantioselectivity. Particularly, the *ortho*-methyl substituents of the substrates could increase the enantioselectivity. The achieved excellent enantioselectivities may be due to the corresponding substrate matches well fitting the chiral space created by the chiral palladium(II)-BINAP catalyst. The *ortho*-methyl substituents may improve the fitting of the substrate match to the chiral space created by the chiral catalyst, hence the enantioselectivity is improved. When using dienes (1,4-diisopropenylbenzene and 1,3-diisopropenylbenzene) as substrates in this reaction, only one of the two carbon-carbon double bonds participated into the reaction affording tetrafunctional organic compounds with moderate enantioselectivities of up to 83.8% *ee*. The chiral Lewis acid palladium(II) catalyst incorporating (*R*)-BINAP, which is a conformationally restricted chiral ligand, is very stable in ionic liquids and could be recycled 21 times with retention of the high enantioselectivity.

Keywords: alkenes; arylglyoxals; carbonyl-ene reaction; enantioselectivity; palladium

Introduction

As one of the most fundamental carbon-carbon bond-forming reactions in organic synthesis and asymmetric catalysis to prepare optically active homoallylic alcohols, the enantioselective carbonyl-ene reaction has attracted much attention in the past two decades, and various transition metal catalysts incorporated with different ligands have been actively studied.[1–7] Some of them could achieve high enantioselectivity, such as organoaluminum catalysts,[1] Ti-BINOL catalysts[2] Cu-BOX catalysts,[4] optically active β-ketoiminato cationic cobalt(III) catalysts,[5] a group of Pd(II)-diphosphine catalysts,[6] and scandium(III) catalysts.[7] For the group of Pd(II)-diphosphine catalysts, Mikami[6a] and co-workers firstly studied the palladium(II) complexes of (*S*)-BINAP, (*S*)-Tol-BINAP and (*S*)-xylyl-BINAP in the glyoxylate-ene reactions between ethyl glyoxylate and alkenes, and demonstrated that $\{Pd(CH_3CN)_2[(S)\text{-Tol-BINAP}]\}(SbF_6)_2$ is an efficient catalyst for the reaction between ethyl glyoxylate and methylenecyclohexane to give (*S*)-ethyl 3-(1′-cyclohexenyl)-2-hydroxypropionate with 78% *ee* and 88% yield at room temperature. Mikami[6b] and co-workers also reported that the chirally dynamic diphenylphosphinoferrocene(DPPF) ligand can be used to prepare enantio- and diastereomerically pure metal complexes by coordination with enantiopure diaminobinaphthyl (DABN) to control the axial chirality of DPPF-M complexes, and demonstrated that Ni(II)-DPPF with DABN affords much higher enantioselectivities for the glyoxylate-ene reactions in comparison with the Pd(II) and Pt(II) counterparts. Soon after that, Gagné[6c] and co-workers reported that $\{[(S)\text{-MeOBIPHEP}]Pt\}(X)_2$ ($X = OTf^-$, SbF_6^-) were also efficient and enantioselective catalysts for the glyoxylate-ene reaction between ethyl glyoxylate and methylenecyclohexane with *ee*s up to 85%, and the addition of achiral acidic phenol additives could increase the rate of the OTf-based catalysts by disrupting contact ion pairs and sequestering traces of water. Gagné[6d] and co-workers also reported that the

platinum complex of *tropos*-BIPHEP [BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl] can be resolved with (*S*)-BINOL, thus the δ- and λ-{(BIPHEP)Pt[(*S*)-BINOL]} systems could each be isolated to give the corresponding single diastereoismer from which the Lewis acid fragments δ- and λ-$[(BIPHEP)Pt]^{2+}$ can be obtained by liberating (*S*)-BINOL *via* different methods. The obtained Pt(II)-BIPHEP Lewis acid is an efficient and enantioselective catalyst for the carbonyl-ene reactions of ethyl glyoxylate and phenylglyoxal with alkenes affording *ee* values as high as 94%[6e] since the coordination of BIPHEP to the substitution-inert metal platinum(II) significantly slows the atropinversion. Recently Doherty[6f] and co-workers reported that the enantiopure platinum(II) complexes of conformationally flexible NUPHOS diphosphines, δ- and λ-$[(NUPHOS)Pt](X)_2$ ($X = OTf^-$, SbF_6^-) are highly efficient catalysts for the carbonyl-ene reactions of ethyl glyoxylate and phenylglyoxal with various alkenes affording *ee* values as high as 95%; The *in situ* activation of δ- and λ-{(NUPHOS)Pt[(*S*)-BINOL]} with triflic acid generated a most efficient catalyst in the ionic liquid $[EMIM][NTf_2]$ [1-ethyl-2-methylimidazolium bis(trifluoromethylsulfonyl)-amide] affording marked enhancements in enantioselectivity compared with the corresponding reactions in dichloromethane; Particularly, platinum(II) catalysts based on monocyclic NUPHOS can compete with their BINAP counterparts.

Homogeneous asymmetric catalysis using chiral Lewis acid catalysts has the evident advantages of high efficiency and high enantioselectivity. However, most homogeneous catalysts for asymmetric reactions are not practical because the chiral catalysts are very expensive and the catalyst loadings are very high, normally 2 mol% to 20 mol%. Therefore recycling the expensive chiral catalysts is extremely important for industrial applications. Beside heterogenization of homogeneous catalysts to make solid catalysts which usually results in decreased enantioselectivity and/or activity, recently some reports have demonstrated that ionic liquids could be used to recycle the chiral catalysts by phase separation for five cycles with retention of high enantioselectivities and good activities.[8] Jessop[8a] and co-workers reported that the asymmetric hydrogenation of tiglic acid in $[BMIM]PF_6/H_2O$ (BMIM = 1-butyl-3-methylimidazolium) gave 85% *ee*. After the product had been extracted with $scCO_2$, the ionic liquid-immobilized catalyst was reused for four times with an average *ee* of 89% which is higher than the original *ee* of 85% obtained from the first cycle; at the same time the conversion dropped only slightly from 99% to 97%. Song[8b] and co-workers reported that a chiral (salen)Mn catalyst could be recycled for four times in $[BMIM][PF_6]$ for the asymmetric epoxidation of 2,2-dimethylchromene, after five cycles, the *ee* dropped from 96% to 88%, and the yield dropped from 86% to 53%. Ohta[8c] and co-workers reported that, in the asymmetric transfer hydrogenation of acetophenone, the Lewis acid catalyst TsDPEN-coordinated Ru(II) complex [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] could be recycled in $[BMIM][PF_6]$ through five cycles. Although the conversion evidently decreased from 96% to 63%, the high enantioselectivity (93% *ee*) remained constant. Concerning catalyst recycle for enantioselective carbonyl-ene reactions, Ikegami[2d] and co-workers developed a reusable heterogeneous catalyst prepared from a self-assembly of $Ti(O\text{-}i\text{-}Pr)_4$ and non-cross-linked copolymers with (*R*)-BINOL pendant groups, which was reused four times for the enantioselective carbonyl-ene reaction between ethyl glyoxylate and α-methylstyrene with almost no loss of activity (around 85% yield), but the *ee* dropped from 88% to 81%. Particularly, Doherty[6f] and co-workers have demonstrated that the *in situ* generated δ-$[(NUPHOS)Pt](OTf)_2$ from BINOLate precursors can be used three times with almost no loss of enantioselectivity in the ionic liquid $[EMIM][NTf_2]$, although the isolated yields dropped evidently. For example, for the monocyclic NUPHOS-Pt(II)-catalyzed reaction between phenylglyoxal and methylenecyclohexane, the enantioselectivity remained constant (87% *ee*, 87% *ee*, 86% *ee* for three cycles, respectively), but the isolated yields dropped from 38% to 13% over these three cycles; For the reaction between ethyl glyoxylate and methylenecyclohexane, the enantioselectivity also remained constant (71% *ee*, 70% *ee*, 70% *ee* for three cycles, respectively), but the isolated yield also dropped from 74% to 43% over these cycles.

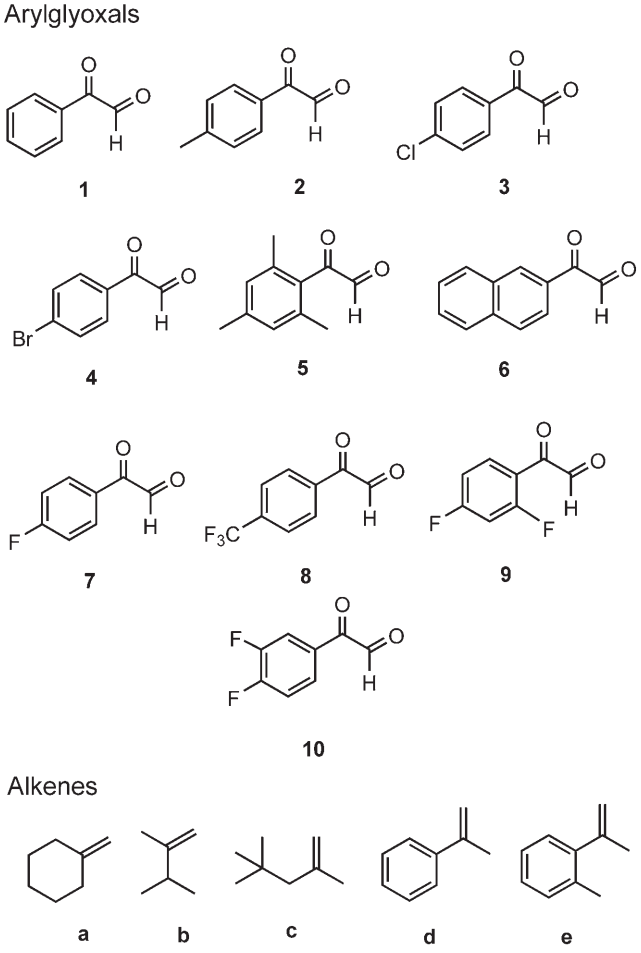
Because all of the catalysts were reported to be water-sensitive, strictly anhydrous reaction conditions are needed, including drying of solvents, substrates and reactors, etc. One of the two substrates is an arylglyoxal that is usually prepared, purified and transported as the monohydrate form.[9] The dry arylglyoxal has to be prepared by drying the arylglyoxal monohydrate under vacuum and at elevated temperature because the chiral catalysts are water-sensitive. This caused much inconvenience in the study of enantioselective carbonyl-ene reactions and, as a consequence, only phenylglyoxal was studied. Recently, we found that palladium(II)- and platinum(II)-BINAP catalysts are water-tolerant in the enantioselective carbonyl-ene reactions, so the arylglyoxal monohydrate could be used directly as substrate achieving good to excellent enantioselectivities.[10] This provided us with a versatile and convenient method to study different arylglyoxals in this reaction, to investigate the effect of substrates systematically by matching arylglyoxals integrated with alkenes. In the present studies, we systematically investigated the Pd(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions of ten aryl-

glyoxals with five alkenes and two dienes. The effect of the substrates on enantioselectivity is discussed; We also studied the recycle of the palladium(II) catalyst with (*R*)-BINAP that is a conformationally restricted chiral diphosphine ligand in the ionic liquid [BdMIM][NTf_2], and proved that the Pd(II)-BINAP catalyst is very stable in [BdMIM][NTf_2] and can be recycled 21 times with retention of the high enantioselectivity and no loss of isolated yield for the first 11 cycles.

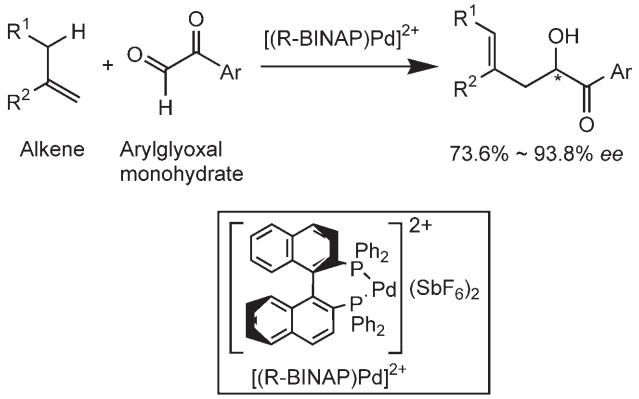
Results

Pd(II)-BINAP-Catalyzed Enantioselective Carbonyl-Ene Reactions between Ten Arylglyoxals and Five Alkenes

In order to study the effect of the substrates, here we selected ten arylglyoxals and five alkenes with different molecular structures. The ten arylglyoxals include phenylglyoxal, 4-methylphenylglyoxal, 4-chlorophenylglyoxal, 4-bromophenylglyoxal, 2,4,6-trimethylphenylglyoxal, 2-naphthylglyoxal, 4-fluorophenylglyoxal, 4-trifluoromethylphenylglyoxal, 2,4-difluorophenylglyoxal and 3,4-difluorophenylglyoxal (**1–10** in Scheme 1). The five alkenes include methylenecyclohexane, 2,3-dimethyl-1-butene, 2,4,4-trimethyl-1-pentene, α-methylstyrene and α,2-dimethylstyrene (**a–e** in Scheme 1). The Pd(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions between the above ten arylglyoxals and the five alkenes were systematically investigated and demonstrated good to excellent enantioselectivities with *ee* values between 72.8% and 93.8% (Table 1 and Scheme 2). Both the arylglyoxals and the alkenes could evidently affect the enantioselectivity, indicating that the Pd(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions are highly substrate-dependent. In general, the reactions of both 2,3-dimethyl-1-butene and α,2-dimethylstyrene demonstrate excellent enantioselectivities with all the ten arylglyoxals (entries 11–20 and 41–50). The reactions of both methylenecyclohexane and 2,4,4-trimethyl-1-pentene demonstrate relatively lower but still high enantioselectivities (1–10 and 21–30), while the reactions of α-methylstyrene demonstrate the lowest enantioselectivities (entries 31–40).



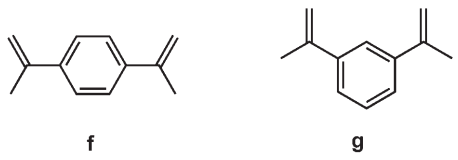
Scheme 1. Substrates employed in the enantioselective carbonyl-ene reactions.



Scheme 2. Enantioselective carbonyl-ene reactions catalyzed by the chiral catalyst {[(*R*)-BINAP]Pd}(SbF_6)$_2$.

Enantioselective Carbonyl-Ene Reactions of Dienes

Two dienes, 1,4-diisopropenylbenzene and 1,3-diisopropenylbenzene (**f** and **g** in Scheme 3) were investi-



Scheme 3. Structures of 1,4-diisopropenylbenzene and 1,3-diisopropenylbenzene.

Table 1. Enantioselective carbonyl-ene reactions of ten arylglyoxals with five alkenes.[a]

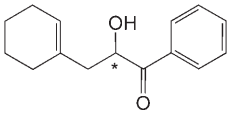
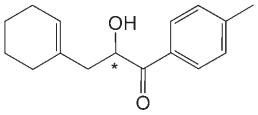
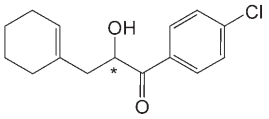
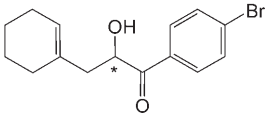
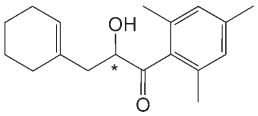
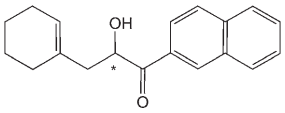
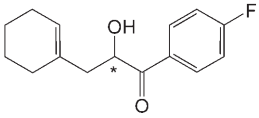
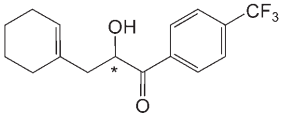
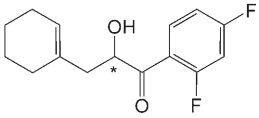
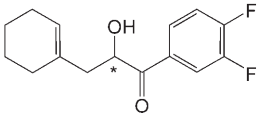
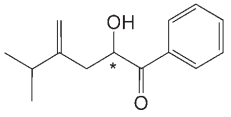
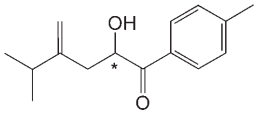
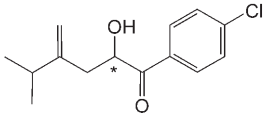
Entry	Alkene	Arylglyoxal	Product No.	Structure	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	**a**	**1**	**1a**		1	51	88.0 (*S*)
2	**a**	**2**	**2a**		1	47	85.5 (*S*)
3	**a**	**3**	**3a**		2	35	85.2 (*S*)
4	**a**	**4**	**4a**		3	39	84.2 (*S*)
5	**a**	**5**	**5a**		2	41	91.2 (*S*)
6	**a**	**6**	**6a**		2	50	73.6 (*S*)
7	**a**	**7**	**7a**		2	43	87.8 (*S*)
8	**a**	**8**	**8a**		2	41	86.0 (*S*)
9	**a**	**9**	**9a**		1.5	42	85.0 (*S*)
10	**a**	**10**	**10a**		2	37	85.2 (*S*)
11	**b**	**1**	**1b**		2	50	93.0 (*S*)
12	**b**	**2**	**2b**		1	37	91.8 (*S*)
13	**b**	**3**	**3b**		2	43	91.6 (*S*)

Table 1. (Continued)

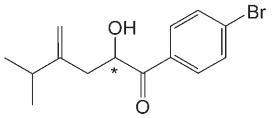
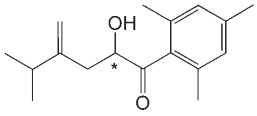
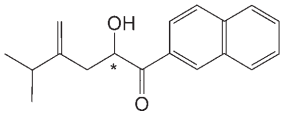
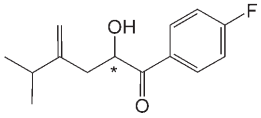
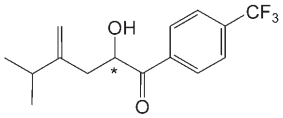
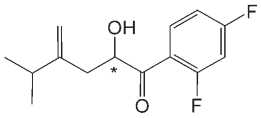
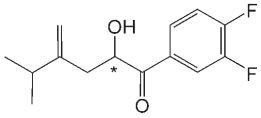
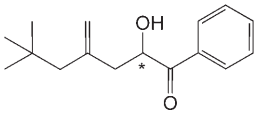
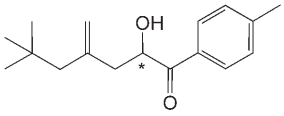
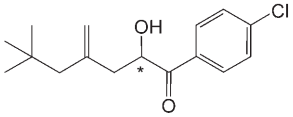
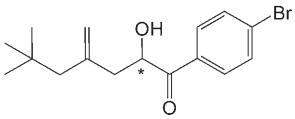
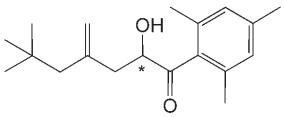
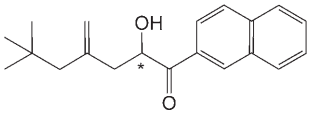
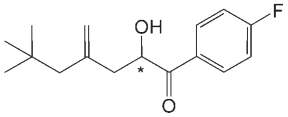
Entry	Alkene	Arylglyoxal	Product No.	Structure	Time [h]	Yield[b] [%]	*ee*[c] [%]
14	**b**	**4**	**4b**		3	35	89.5 (*S*)
15	**b**	**5**	**5b**		2	50	93.4 (*S*)
16	**b**	**6**	**6b**		2	34	91.6 (*S*)
17	**b**	**7**	**7b**		2	34	92.8 (*S*)
18	**b**	**8**	**8b**		2	41	92.0 (*S*)
19	**b**	**9**	**9b**		2	30	91.8 (*S*)
20	**b**	**10**	**10b**		2	34	91.6 (*S*)
21	**c**	**1**	**1c**		2	56	88.0 (*S*)
22	**c**	**2**	**2c**		1	49	86.8 (*S*)
23	**c**	**3**	**3c**		3	59	76.4 (*S*)
24	**c**	**4**	**4c**		3	46	85.1 (*S*)
25	**c**	**5**	**5c**		2	36	92.6 (*S*)
26	**c**	**6**	**6c**		2	48	84.0 (*S*)
27	**c**	**7**	**7c**		2	37	87.2 (*S*)

Table 1. (Continued)

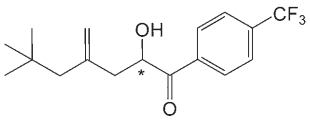
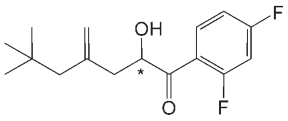
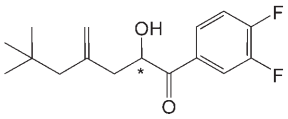
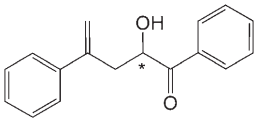
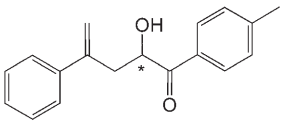
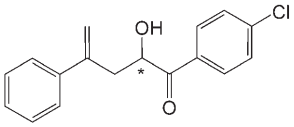
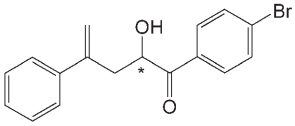
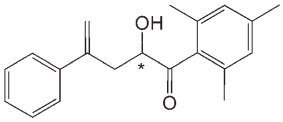
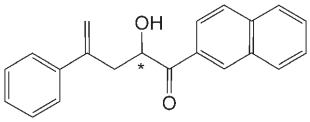
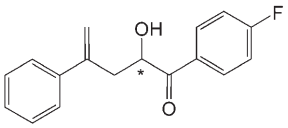
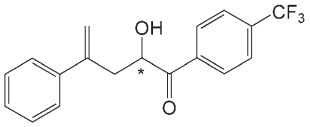
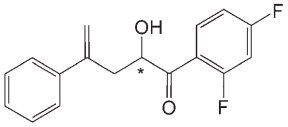
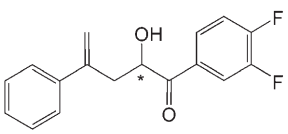
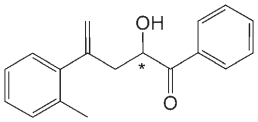
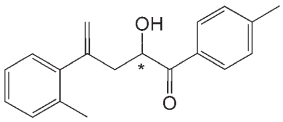
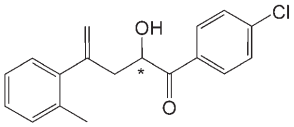
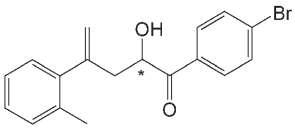
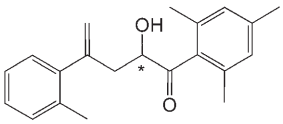
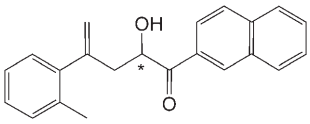
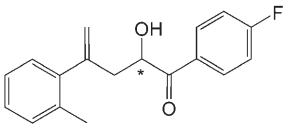
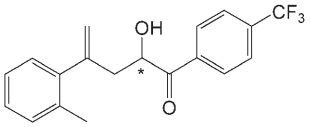
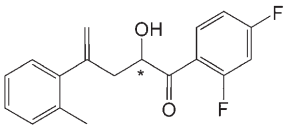
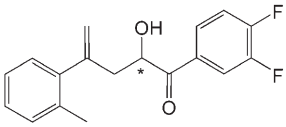
Entry	Alkene	Arylglyoxal	Product No.	Structure	Time [h]	Yield[b] [%]	*ee*[c] [%]
28	**c**	**8**	**8c**		2	51	85.0 (*S*)
29	**c**	**9**	**9c**		1.5	41	87.3 (*S*)
30	**c**	**10**	**10c**		2	46	81.8 (*S*)
31	**d**	**1**	**1d**		1	40	80.0 (*S*)
32	**d**	**2**	**2d**		1	32	82.8 (*S*)
33	**d**	**3**	**3d**		1	31	74.8 (*S*)
34	**d**	**4**	**4d**		0.5	33	76.0 (*S*)
35	**d**	**5**	**5d**		0.5	20	75.2 (*S*)
36	**d**	**6**	**6d**		0.5	21	78.4 (*S*)
37	**d**	**7**	**7d**		0.5	22	78.0 (*S*)
38	**d**	**8**	**8d**		0.5	27	75.0 (*S*)
39	**d**	**9**	**9d**		0.5	17	82.4 (*S*)
40	**d**	**10**	**10d**		0.5	18	72.8 (*S*)

Table 1. (Continued)

Entry	Alkene	Arylglyoxal	Product No.	Structure	Time [h]	Yield[b] [%]	*ee*[c] [%]
41	**e**	**1**	**1e**		0.5	21	93.6 (*S*)
42	**e**	**2**	**2e**		0.5	22	93.8 (*S*)
43	**e**	**3**	**3e**		0.5	25	93.0 (*S*)
44	**e**	**4**	**4e**		0.5	21	93.6 (*S*)
45	**e**	**5**	**5e**		0.5	35	92.8 (*S*)
46	**e**	**6**	**6e**		0.5	22	93.6 (*S*)
47	**e**	**7**	**7e**		0.5	19	93.8 (*S*)
48	**e**	**8**	**8e**		0.5	18	91.4 (*S*)
49	**e**	**9**	**9e**		0.5	28	93.6 (*S*)
50	**e**	**10**	**10e**		0.5	16	90.0 (*S*)

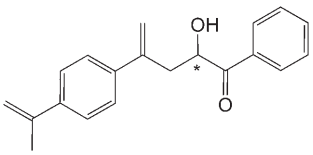
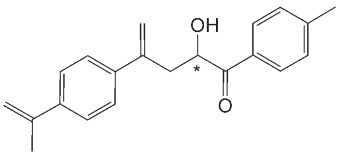
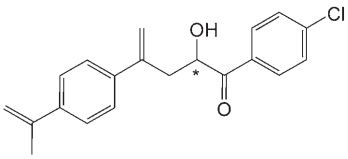
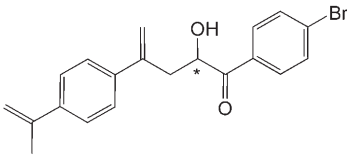
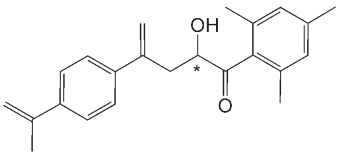
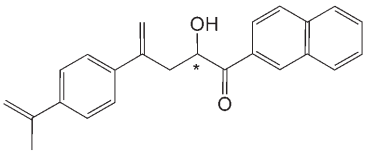
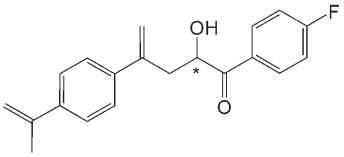
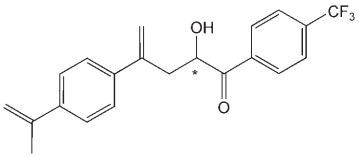
[a] *Reaction conditions:* All the reactions were run under room temperature. Catalyst {[(*R*)-BINAP]Pd}$(SbF_6)_2$, 0.0125 mmol (5 mol%); arylglyoxal monohydrate, 0.25 mmol; alkene, 0.25 mmol.

[b] Isolated yield with flash chromatography.

[c] Determined by HPLC with a Chiralcel OD-H column for products **1a**, **2a**, **1b**, **2b**, **1c**, **2c**; with a Chiralpak AD-H column for products **3a**, **4a**, **3b**, **4b**, **3c**, **4c**, **8c**, **9c**; with a Chiralpak AS-H column for products **5a–10a**, **5b–10b**, **5c–7c**, **10c**, **5d–10d**; with a Chiralcel OB-H column for products **1d**, **2d**, **3d**, **4d**. The absolute configurations of the carbonyl-ene products were determined by comparing the HPLC retention times with those reported in the literature, or by comparison with the analogous products reported in the literature.

gated in the enantioselective carbonyl-ene reactions. The results revealed that only one of the two carbon-carbon double bonds of the diene participated in the reaction affording tetrafunctional organic compounds with moderate enantioselectivities (see Table 2 and Table 3). Even when the molar ratio of arylglyoxal to

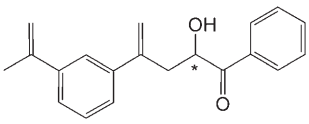
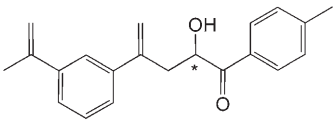
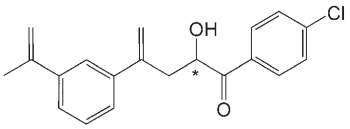
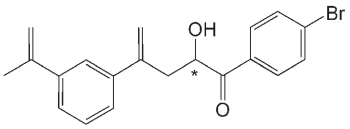
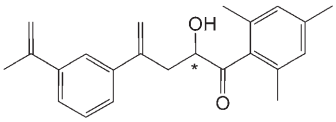
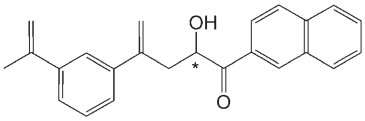
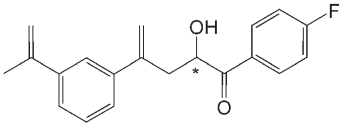
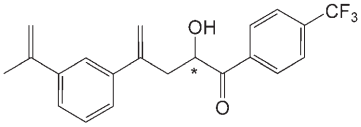
Table 2. Enantioselective carbonyl-ene reactions between arylglyoxals and 1,4-diisopropenylbenzene.[a]

Entry	Arylglyoxal	Product No.	Structure	Time	Yield[b] [%]	*ee*[c] [%]
1	**1**	**1f**		30 min	23	72.4 (*S*)
2	**2**	**2f**		30 min[d]	9	66.0 (*S*)
3	**3**	**3f**		15 min	29	73.8 (*S*)
4	**4**	**4f**		20 min	18	68.8 (*S*)
5	**5**	**5f**		10 min	15	67.2 (*S*)
6	**6**	**6f**		10 min	13	74.4 (*S*)
7	**7**	**7f**		10 min	18	65.8 (*S*)
8	**8**	**8f**		15 min	28	71.3 (*S*)

[a] *Reaction conditions:* All the reactions were run at room temperature. Catalyst {[(*R*)-BINAP]Pd}$(SbF_6)_2$ 0.0125 mmol (5 mol%); arylglyoxal monohydrate, 0.25 mmol; diene, 0.25 mmol.
[b] Isolated yield with flash chromatography.
[c] Determined by HPLC with a Chiralpak AS-H column. The absolute configurations of the carbonyl-ene products were determined by comparing with the analogous product reported in the literature.
[d] Reaction at 0 °C.

diene is as high as 3 to give the arylglyoxal in a large excess, the second carbon-carbon double bond still cannot participate in the reaction. This may be due to the close vicinity of the two carbon-carbon double bonds in the diene. Furthermore, the enentioselectivities remain almost the same when the substrate molar ratio was varied from 1 to 3 (see Table 4). In comparison, diene **g** with a *meta*-disubstituted phenyl group

Table 3. Enantioselective carbonyl-ene reactions between arylglyoxals and 1,3-diisopropenylbenzene.[a]

Entry	Arylglyoxal	Product No.	Structure	Time	Yield[b] [%]	*ee*[c] [%]
1	**1**	**1g**		30 min	36	80.0 (*S*)
2	**2**	**2g**		50 min[d]	16	83.8 (*S*)
3	**3**	**3g**		10 min	23	78.4 (*S*)
4	**4**	**4g**		10 min	21	78.0 (*S*)
5	**5**	**5g**		10 min	41	80.2 (*S*)
6	**6**	**6g**		10 min	21	82.8 (*S*)
7	**7**	**7g**		15 min	20	77.0 (*S*)
8	**8**	**8g**		15 min	27	74.7 (*S*)

[a] *Reaction conditions:* All the reactions were run at room temperature. Catalyst {[(*R*)-BINAP]Pd}$(SbF_6)_2$ 0.0125 mmol (5 mol%); arylglyoxal monohydrate, 0.25 mmol; diene, 0.25 mmol.
[b] Isolated yield with flash chromatography.
[c] Determined by HPLC with a Chiralpak AS-H column. The absolute configurations of the carbonyl-ene products were determined by comparing with the analogous product reported in the literature.
[d] Reaction at 0 °C.

shows higher enantioselectivity than diene **f** with a *para*-disubstituted phenyl group (average *ee* with eight glyoxals in Table 3 and Table 2: 79.4% *vs.* 70.0%). This may be because the two *meta*-isopropenyl substituents in diene **g** are much closer than the two *para*-isopropenyl substituents in diene **f**. Hence in diene **g** when one isopropenyl is participating in the reaction with arylglyoxal, the other isopropenyl is close to the reaction site and therefore shows higher influence to afford higher enantioselectivity.

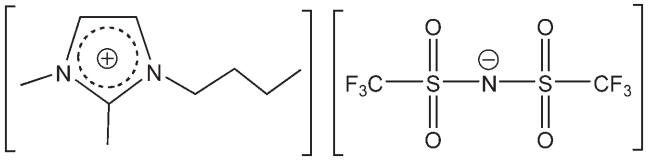
Catalyst Recycle in Ionic Liquid

[BdMIM][NTf_2] [1-butyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl) amide, see Scheme 4] is a more chemically inert room temperature ionic liquid compared with "C-2-unmodified" imidazolium-based ionic liquids,[11a] such as [BMIM][NTf_2] and [EMIM][NTf_2]. In order to minimize the negative effect of the ionic liquid on the reaction, here we selected [BdMIM][NTf_2] as reaction medium to recycle the expensive chiral catalyst {[(*R*)-BINAP]Pd}$(SbF_6)_2$ (see Scheme 2). Three reactions of phenylglyoxal with three alkenes including methylenecyclohexane, 2,3-di-

Table 4. Variation of substrate ratio (n) in enantioselective carbonyl-ene reactions between phenylglyoxal and 1,4-diisopropenylbenzene/1,3-diisopropenylbenzene.[a]

Substrates	Entry	Phenylglyoxal/ Diene (n)	Yield[b] [%]	*ee*[c] [%]
Phenylglyoxal/1,4-diisopropenylbenzene	1	1	23	72.4
	2	2	29	72.8
	3	3	43	72.4
Phenylglyoxal/1,3-diisopropenylbenzene	4	1	36	80.0
	5	2	41	80.2
	6	3	38	80.0

[a] *Reaction conditions:* All the reactions were run at room temperature for 30 min. Catalyst {[(*R*)-BINAP]Pd}-$(SbF_6)_2$ 0.0125 mmol (5 mol%); diene, 0.25 mmol.
[b] Isolated yield with flash chromatography.
[c] Determined by HPLC with a Chiralpak AS-H column.



Scheme 4. Schematic structure of the ionic liquid [BdMIM]-$[NTf_2]$.

methyl-1-butene and 2,4,4-trimethyl-1-pentene, were investigated.

All the three reactions were recycled 21 times. For the reaction between phenylglyoxal and methylenecyclohexane, after the catalyst being recycled for 21 times, the *ee* had only slightly dropped from 87.4% to 86.4%, the yield had cumulated up to 781%, while the turnover had cumulated up to 156.5 mol product/(mol catalyst) (see Table 5 and Figure 1). For the reaction between phenylglyoxal and 2,3-dimethyl-1-butene, the *ee* had slightly dropped from 91.8% to

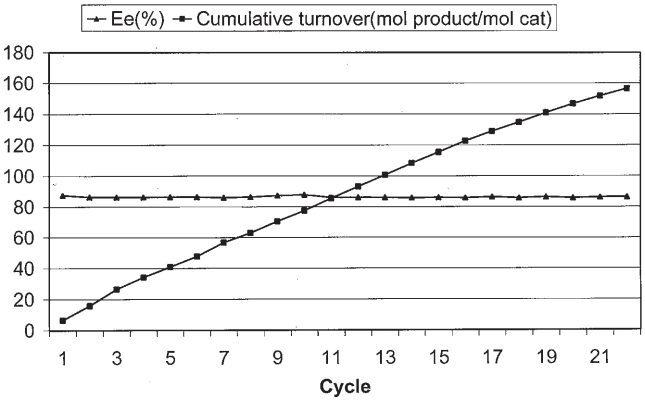


Figure 1. The correlation of *ee* and cumulative turnover with the number of cycle for enantioselective carbonyl-ene reaction between phenylglyoxal monohydrate and methylenecyclohexane in $[BdMIM][NTf_2]$.

91.0% after 22 cycles, the yield had cumulated up to 808%, while the turnover had cumulated up to 161.6 mol product/(mol catalyst) (see Table 6 and Figure 2). For the reaction between phenylglyoxal and 2,4,4-trimethyl-1-pentene, the *ee* remained the same (85.8%) over 22 cycles, the yield had cumulated up to 1057% and the turnover had cumulated up to 211.4 mol product/(mol catalyst) (see Table 7 and Figure 3). It can be concluded that, for all the three reactions, the Pd(II)-BINAP catalyst can be recycled many times (up to 22 cycles) with retention of the high enantiose-

Table 5. Catalyst recycle in $[BdMIM][NTf_2]$ for enantioselective carbonyl-ene reaction between phenylglyoxal monohydrate and methylenecyclohexane.[a]

Cycle	1	2	3	4	5	6	7	8	9	10	11
ee [%][b]	87.4	86.3	86.2	86.2	86.4	86.4	86.0	86.4	87.2	87.8	86.0
Yield [%][c]	33	46	53	39	33	34	45	31	38	34	40
Cumulative Yield [%]	33	79	132	171	204	238	283	314	352	386	426
Turnover	6.6	9.2	10.7	7.7	6.6	6.8	9.0	6.3	7.6	6.9	8.1
Cumulative Tunover	6.6	15.8	26.5	34.2	40.8	47.6	56.6	62.9	70.5	77.4	85.5
Cycle	12	13	14	15	16	17	18	19	20	21	22
ee [%][b]	86.1	86.0	85.8	86.0	85.8	86.4	85.8	86.4	85.8	86.2	86.4
Yield [%][c]	38	38	38	35	37	31	28	31	29	26	24
Cumulative Yield [%]	464	502	540	575	612	643	671	702	731	757	781
Turnover	7.6	7.5	7.7	7.1	7.3	6.3	5.7	6.2	5.7	5.1	4.8
Cumulative Tunover	93.1	100.6	108.3	115.4	122.7	129.0	134.7	140.9	146.6	151.7	156.5

[a] *Reaction conditions:* All the reactions were run under room temperature for 1 hour. Catalyst {[(*R*)-BINAP]Pd}$(SbF_6)_2$, 0.0125 mmol (5 mol%); phenylglyoxal monohydrate, 0.25 mmol; methylenecyclohexane, 0.25 mmol; ionic liquid $[BdMIM][NTf_2]$, 0.5 mL.
[b] Determined by HPLC with a Chiralcel OD-H column.
[c] Isolated yield with flash chromatography.

Table 6. Catalyst recycle in [BdMIM][NTf_2] for enantioselective carbonyl-ene reaction between phenylglyoxal monohydrate and 2,3-dimethyl-1-butene.[a]

Cycle	1	2	3	4	5	6	7	8	9	10	11
ee [%][b]	91.8	91.8	91.6	91.6	91.8	91.6	91.6	91.6	91.6	91.4	91.2
Yield [%][c]	36	44	46	48	46	49	51	41	41	39	37
Cumulative Yield [%]	36	80	126	174	220	269	320	361	402	441	478
Turnover	7.2	8.8	9.2	9.6	9.2	9.8	10.2	8.2	8.2	7.8	7.4
Cumulative Tunover	7.2	16.0	25.2	34.8	44.0	53.8	64.0	72.2	80.4	88.2	95.6
Cycle	12	13	14	15	16	17	18	19	20	21	22
ee [%][b]	91.9	92.0	91.4	91.5	91.6	91.7	91.8	91.6	91.6	91.9	91.0
Yield [%][c]	35	34	34	34	32	30	29	28	27	26	21
Cumulative Yield [%]	513	547	581	615	647	677	706	734	761	787	808
Turnover	7.0	6.8	6.8	6.8	6.4	6.0	5.8	5.6	5.4	5.2	4.2
Cumulative Tunover	102.6	109.4	116.2	123.0	129.4	135.4	141.2	146.8	152.2	157.4	161.6

[a] *Reaction conditions:* All the reactions were run under room temperature for 2 h. Catalyst {[(*R*)-BINAP]Pd}$(SbF_6)_2$, 0.0125 mmol (5 mol%); phenylglyoxal monohydrate, 0.25 mmol; 2,3-dimethyl-1-butene, 0.25 mmol; ionic liquid [BdMIM][NTf_2], 1.0 mL.
[b] Determined by HPLC with a Chiralcel OD-H column.
[c] Isolated yield with flash chromatography.

lectivity; the isolated yield did not drop for the first 11 cycles and then dropped slowly for the second 11 cycles. These results clearly show that immobilizing conformationally stable chiral Lewis acid catalysts in chemically inert ionic liquids is a powerful strategy to recycle expensive chiral catalysts, combining the advantages of homogeneous and heterogeneous catalysis. To improve the recycling of δ-[(NUPHOS)Pt]$(OTf)_2$ in the ionic liquid [EMIM][NTf_2] for three cycles,[6f] in the present catalyst recycle studies we focused on the following points: 1) We selected the cheaper metal palladium instead of platinum. 2) (*R*)-BINAP is a conformationally restricted ligand that does not have the problem of racemization in the re-

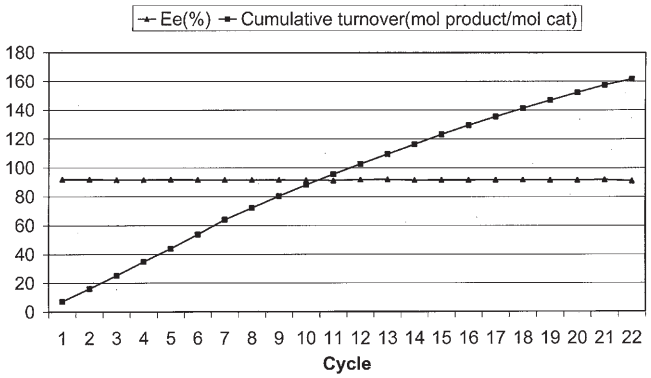


Figure 2. The correlation of *ee* and cumulative turnover with the number of cycles for enantioselective carbonyl-ene reaction between phenylglyoxal monohydrate and 2,3-dimethyl-1-butene in [BdMIM][NTf_2].

Table 7. Catalyst recycle in [BdMIM][NTf_2] for enantioselective carbonyl-ene reaction between phenylglyoxal monohydrate and 2,4,4-trimethyl-1-pentene.[a]

Cycle	1	2	3	4	5	6	7	8	9	10	11
ee [%][b]	85.8	86.2	86.0	85.6	86.1	86.2	85.4	84.8	85.6	86.0	85.6
Yield [%][c]	50	58	54	56	56	52	54	54	51	51	52
Cumulative Yield [%]	50	108	162	218	274	326	380	434	485	536	588
Turnover	10.0	11.6	10.8	11.2	11.2	10.4	10.8	10.8	10.2	10.2	10.4
Cumulative Tunover	10.0	21.6	32.4	43.6	54.8	65.2	76.0	86.8	97.0	107.2	117.6
Cycle	12	13	14	15	16	17	18	19	20	21	22
ee [%][b]	85.6	85.2	86.0	86.0	86.2	86.2	86.0	86.0	86.4	85.8	85.8
Yield [%][c]	50	48	45	43	47	39	42	41	41	38	35
Cumulative Yield [%]	638	686	731	774	821	860	902	943	984	1022	1057
Turnover	10.0	9.6	9.0	8.6	9.4	7.8	8.4	8.2	8.2	7.6	7.0
Cumulative Tunover	127.6	137.2	146.2	154.8	164.2	172.0	180.4	188.6	196.8	204.4	211.4

[a] *Reaction conditions:* All the reactions were run under room temperature for 2 h. Catalyst {[(*R*)-BINAP]Pd}$(SbF_6)_2$, 0.0125 mmol (5 mol%); phenylglyoxal monohydrate, 0.25 mmol; 2,4,4-trimethyl-1-pentene, 0.25 mmol; ionic liquid [BdMIM][NTf_2], 1.0 mL.
[b] Determined by HPLC with a Chiralcel OD-H column.
[c] Isolated yield with flash chromatography.

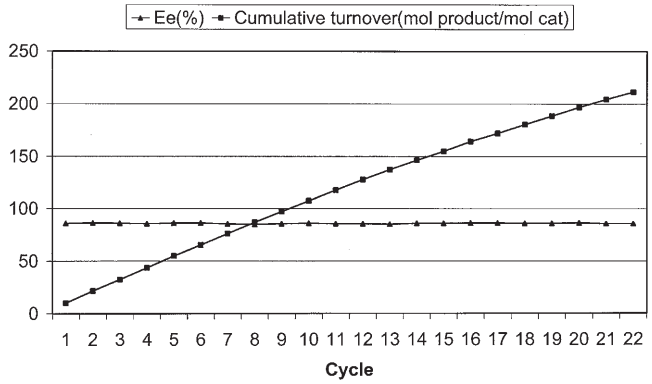


Figure 3. The correlation of *ee* and cumulative turnover with the number of cycles for enantioselective carbonyl-ene reaction between phenylglyoxal monohydrate and 2,4,4-trimethyl-1-pentene in [BdMIM][NTf_2].

cycling process comparing with *tropos*- or conformationally flexible ligands.[6d,f] 3) The ionic liquid [BdMIM][NTf_2] is a more chemically inert ionic liquid compared to "C-2-unmodified" imidazolium-based ionic liquids.[11a] 4) Phenylglyoxal monohydrate was used directly as substrate instead of freshly dried phenylglyoxal. Based on the above four points, we achieved 22 cycles with retention of the high enantioselectivity and no loss of isolated yields for the first 11 cycles. Therefore we have made the Pd(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions more practical, and to the best of our knowledge, this is the best result of catalyst recycle in any enantioselective carbonyl-ene reaction.

For the chiral diphosphine-Pd(II)- and Pt(II)-catalyzed enantioselective carbonyl-ene reactions, in some cases the yields are low.[6] One reason is that the reaction is not fast enough, there are still some unreacted substrates left when terminating the reaction. Another reason is that the product is a multi-functional organic molecule that is very active and could undergo parallel side reactions resulting in the product being consumed. This is supported by the result that a short reaction time (such as 0.5–2 h) usually gives higher yields and more pure products than a long reaction time (such as overnight). In the catalyst recycle studies, although the yield for each reaction cycle is not high, the catalyst recycle of 22 times has made the expensive chiral catalyst much more productive in comparison to the corresponding enantioselective carbonyl-ene reactions in dichloromethane.

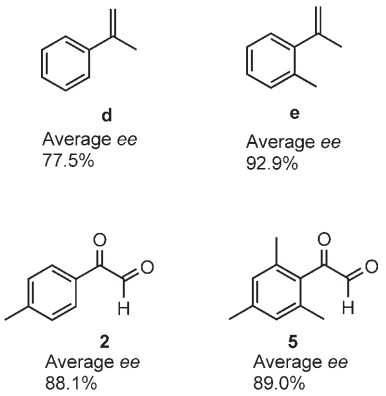
Discussion

The Effect of Substrates

From the enantioselective carbonyl-ene reactions of ten arylglyoxals with five alkenes listed in Table 1, the average *ee* values of one arylglyoxal with five alkenes and one alkene with ten arylglyoxals were calculated and sorted in order from high to low in Table 8 and Table 9, respectively. In comparison, alkenes demonstrate greater influence on the enantioselectivity than arylglyoxals (Δee: 15.4% *vs.* 4.8%). The average *ee*s of the ten arylglyoxals are between 89.0% and 84.2%, the order is arylglyoxal **5** > arylglyoxal **1** > arylglyoxal **2** > arylglyoxal **9** > arylglyoxal **7** > arylglyoxal **8** > arylglyoxal **4** > arylglyoxal **10** > arylglyoxal **3** = arylglyoxal **6**. The average *ee*s of the five alkenes are between 92.9% and 77.5%, the order is alkene **e** > alkene **b** > alkene **c** > alkene **a** > alkene **d**. Among the ten arylglyoxals, 2,4,6-trimethylphenylglyoxal demonstrates the highest average *ee* values of up to 89.0%; Among the five alkenes, α,2-dimethylstyrene demonstrates the highest average *ee* values of up to 92.9%. These results showed that both arylglyoxal and alkene demonstrated evident effects on enantioselectivity.

Table 9. Average *ee* of one alkene with ten arylglyoxals(from high to low).

Alkene	**e**	**b**	**c**	**a**	**d**	Δee
Average *ee*	92.9	91.9	85.4	85.2	77.5	15.4



Scheme 5. The effect of an *ortho*-methyl group.

Table 8. Average *ee* of one arylglyoxal with five alkenes(from high to low).

Arylglyoxal	**5**	**1**	**2**	**9**	**7**	**8**	**4**	**10**	**3**	**6**	Δee
Average *ee*	89.0	88.5	88.1	88.0	87.9	85.9	85.7	84.3	84.2	84.2	4.8

The Effect of *ortho*-Methyl Substituents of Both Arylglyoxals and Alkenes

The average *ee* of α,2-dimethylstyrene is much higher than the average *ee* of α-methylstyrene (92.9% *vs.* 77.5%), clearly indicating that only one *ortho*-methyl substituent could significantly increase the enantioselectivity (Scheme 5). The average *ee* of 2,4,6-trimethylphenylglyoxal is higher than the average *ee* of 4-methylphenylglyoxal (89.0% *vs.* 88.1%), indicating that the two *ortho*-methyl substituents could also increase the enantioselectivity (Scheme 5). The promoting effect of the *ortho*-methyl substituent on enantioselectivity may be due to the close vicinity of the *ortho*-methyl to the reaction site.

Pt(II)-BINAP-Catalyzed Enantioselective Carbonyl-Ene Reactions

In order to further prove the promoting effect of *ortho*-methyl substituent, the Pt(II)-BINAP-catalyzed carbonyl-ene reactions of α-methylstyrene (**d**) and α,2-dimethylstyrene (**e**) with phenylglyoxal (**1**) and 4-methylphenylglyoxal (**2**) were investigated (Table 10). For the reactions with both phenylglyoxal (entries 1 and 2) and 4-methylphenylglyoxal (entries 3 and 4), α,2-dimethylstyrene demonstrates much higher enantioselectivities than α-methylstyrene (90.2% *ee vs.* 78.0% *ee*; 93.0% *ee vs.* 76.2% *ee*). This significant promoting effect of the Pt(II)-BINAP catalyst is highly consistent with that of the Pd(II)-BINAP catalyst.

Table 10. Pt(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions of α-methylstyrene and α,2-dimethylstyrene with phenylglyoxal and 4-methylphenylglyoxal.[a]

Entry	Alkene	Arylglyoxal	Product	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	**d**	**1**	**1d**	2	76	78.0 (*R*)
2	**e**	**1**	**1e**	0.5	70	90.2 (*R*)
3	**d**	**2**	**2d**	1.5	70	76.2 (*R*)
4	**e**	**2**	**2e**	0.5	64	93.0 (*R*)

[a] *Reaction conditions:* All the reactions were run under room temperature. Catalyst {[(*S*)-BINAP]Pt}$(SbF_6)_2$, 0.0125 mmol (5 mol%); arylglyoxal monohydrate, 0.25 mmol; alkene, 0.25 mmol.

[b] Isolated yield with flash chromatography.

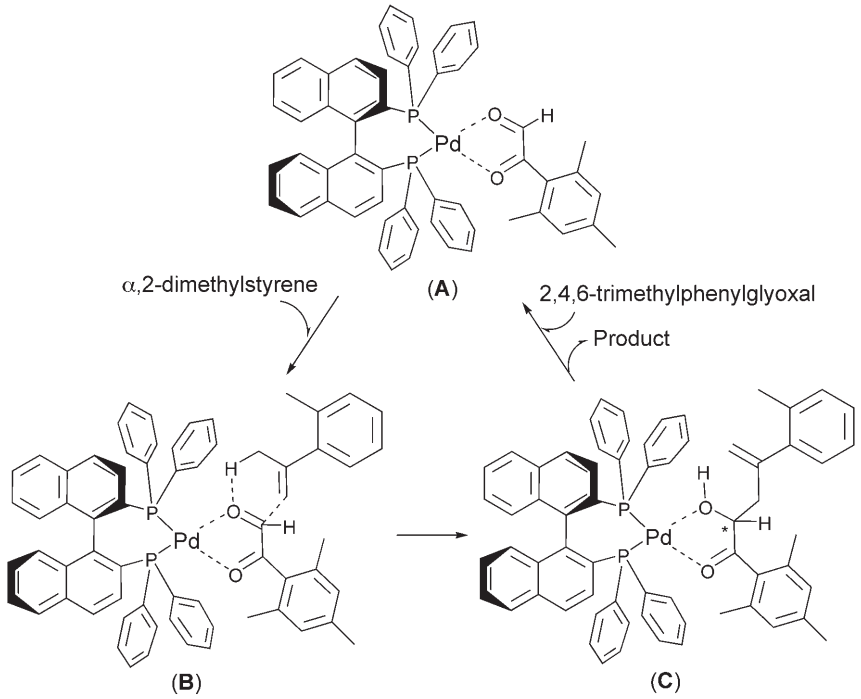
[c] Determined by HPLC with a Chiralcel OB-H column for products **1d**, **2d**; with a Chiralpak AS-H column for products **1e**, **2e**. The absolute configurations of the carbonyl-ene products were determined by comparing the HPLC retention times with those reported in the literature, or by comparing with the analogous products reported in the literature.

Mechanistic Considerations on the Effect of Substrates

Mikami and his co-workers have proposed that the coordination of ethyl glyoxylate with the chiral catalyst forms the key intermediate.[6a] Gagne and his co-workers proposed the same kind of intermediate to interpret the counterion-dependent additive and diphosphine electronic effects.[6c] In order to interpret the substrate effect, here we propose a catalytic cycle (Scheme 6) involving the intermediate (**A**) which is formed from the coordination of the chiral catalyst with arylglyoxal and intermediate (**C**) which is a complex of the chiral catalyst with the product. The substrate effect may be closely related to the fitness of the substrate match to the chiral space created by the chiral catalyst, and better fitness results in higher enantioselectivity. The achieved excellent enantioselectivities of the carbonyl-ene reactions shown in Table 1 may be due to the corresponding substrate matches well fitting the chiral space created by palladium(II)-BINAP catalyst when the alkene is approaching the coordinated arylglyoxal to form the product (**B** in Scheme 6). The intermediate (**C**) releases the chiral product which is an optically active homoallylic alcohol, meanwhile the palladium(II)-BINAP catalyst reverts to intermediate (**A**) by coordinating with arylglyoxal again. The *ortho*-methyl substituents are close to the reaction site and they may improve the fitness of the substrate match to the chiral space, therefore the enantioselectivity is increased. Comparing the arylglyoxals in Scheme 1 revealed that, although both the fluoro substituent which is a strong electron-withdrawing group and the methyl substituent which is an electron-donating group, are attached to the phenyl ring, arylglyoxals **1**, **2**, **9**, **7** have almost the same *ee* values(average *ee* 88.5%, 88.1%, 88.0%, 87.9%, respectively), only the bulky methyl at the o*rtho* position could increase the enantioselectivity(arylglyoxal **5**: average *ee* 89.0%). This may further imply that the promoting effect of *ortho*-methyl group is because of a steric effect, not an electronic effect.

Conclusions

The palladium(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions between ten arylglyoxals and five alkenes were systematically investigated and demonstrated good to excellent enantioselectivities with *ee* values of up to 93.8%. Both arylglyoxals and alkenes demonstrate evident effects on the enantiose-



Scheme 6. Proposed catalytic cycle to interpret the effect of substrates on enantioselectivity in the Pd(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions.

lectivity. The achieved excellent enantioselectivities may be due to the corresponding substrate matches well fitting the chiral space created by the chiral palladium(II)-BINAP catalyst.

The *ortho*-methyl substituents of the substrates could increase the enantioselectivity. This may be due to the fact that the *ortho*-methyl group could improve the fitness of the substrate match to the chiral space created by the chiral catalyst.

Using a diene (1,4-diisopropenylbenzene and 1,3-diisopropenylbenzene) as substrate in the enantioselective carbonyl-ene reactions, only one of the two carbon-carbon double bonds participated in the reaction affording tetrafunctional organic compounds with moderate enantioselectivities of up to 83.8% *ee*.

The chiral Lewis acid Pd(II) catalyst incorporated with (*R*)-BINAP that is a conformationally restricted chiral ligand, is very stable in an ionic liquid; it could be recycled for 21 times with retention of the high enantioselectivity.

Experimental Section

General Considerations

The manipulations were carried out under an atmosphere of nitrogen or argon by using standard Schlenk line techniques. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker 400 spectrometer. Analytical high-performance liquid chromatography (HPLC) was performed on an Agilent 110 Series HPLC equipped with a UV detector using a chiral column selected from Chiralcel OD-H, Chiralcel OB-H, Chiralpak AD-H and Chiralpak AS-H columns. Elemental analysis was performed on a EuroEA3000 Series Elemental Analyzer. Purification of reaction products was carried out by flash column chromatography on silica gel. Phenylglyoxal monohydrate was purchased from Sigma–Aldrich, all the other aryglyoxal monohydrates were purchased from SynChem. All the alkenes including methylenecyclohexane, 2,3-dimethyl-1-butene, 2,4,4-trimethyl-1-pentene, α-methylstyrene and α,2-dimethylstyrene were purchased form Sigma–Aldrich and used without pretreatment. The two dienes, 1,4-diisopropenylbenzene and 1,3-diisopropenylbenzene, were purchased from TCI. The ionic liquid [BdMIM] [NTf_2] was prepared following a reported method.[11]

Catalyst Activation

A small Schlenk flask was charged with 0.0125 mmol [(*R*)-BINAP]$PdCl_2$ and $AgSbF_6$ (2.5 equivs.), after which 2 mL dichloromethane were added. The resulting mixture was stirred for 30 min under a nitrogen or argon atmosphere at room temperature, giving an *in situ* activated catalyst solution of {[(*R*)-BINAP]Pd}$(SbF_6)_2$.

General Procedure for Enantioselective Carbonyl-Ene Reactions

To a solution of the *in situ* prepared catalyst in dichloromethane according to the above described activation method, was added 0.25 mmol of the corresponding arylglyoxal mono-

hydrate and 0.25 mmol of the alkene. The resulting mixture was stirred for required time at room temperature. The reaction mixture was firstly concentrated and then diluted with 1 mL of hexane. The mixture was immediately loaded onto a silica gel column, and eluted with hexane/ethyl acetate mixture to give the corresponding product. The isolated compound was characterized with ^{1}H NMR and ^{13}C NMR ($CDCl_3$, 400 MHz). The enantiomeric excess was determined by HPLC with a chiral column.

General Procedure for Catalyst Recycle in Ionic Liquid

The *in situ* activated catalyst solution in dichloromethane was transferred through a small filter into another small Schlenk flask which was already charged with 0.5 mL or 1 mL of ionic liquid. Then 0.25 mmol of phenylglyoxal monohydrate was added and the resulting mixture was stirred for several minutes until the phenylglyoxal monohydrate had dissolved completely. After removing the dichloromethane under vacuum, 0.25 mmol of alkene was added and the reaction was run for the required time at room temperature. Then the reaction mixture was extracted with ether (2 mL × 3). Removal of the ether gave a residue which was then dissolved into 1.5 mL of hexane/ethyl acetate(9:1), loaded onto a silica gel column, and eluted with hexane/ethyl acetate mixture (9:1) to give the corresponding product. The isolated material was checked with ^{1}H NMR ($CDCl_3$, 400 MHz). The enantiomeric excess was determined by HPLC with a chiral column. After being extracted, the reaction mixture (i.e., ionic liquid layer) was dried under vacuum to remove the residual ether. According to the above procedure, the reaction was repeated for 21 times to evaluate the capabilities of the ionic liquid immobilized chiral catalyst.

Supporting Information

Detailed descriptions of the procedures for the preparation and characterization of products **1a–g**, **2a–g**, **3a–g**, **4a–g**, **5a–g**, **6a–g**, **7a–g**, **8a–g**, **9a–e** and **10a–e** are given in the Supporting Information.

Acknowledgements

This work was supported by Institute of Chemical and Engineering Sciences (ICES) A-STAR, Singapore.

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