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Development of Ruthenium Catalysts for the Enantioselective Synthesis of P-Stereogenic Phosphines via Nucleophilic Phosphido Intermediates

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Abstract: This work details the development of ruthenium(II) catalysts for the enantioselective alkylation of chiral racemic secondary phosphines. The reactions proceed through the intermediacy of nucleophilic phosphido species, which have low barriers to pyramidal inversion; this allows for a dynamic kinetic asymmetric alkylation. The initially discovered [((*R*)-*i*Pr-PHOX)$_2$Ru(H)][BPh$_4$] (**6**) catalyst was found to be effective in the reaction with benzylic chlorides; moreover, the alkylation displayed an unusual temperature dependence. However, the limited scope of alkylation of **6** motivated further studies which led to the development of two complementary chiral mixed ligand Ru(II) catalysts of type [L^{1}L^{2}Ru(H)]$^+$. These catalysts were derived from a combination of one chiral and one achiral ligand, where a synergistic interaction of the two ligands creates an effective asymmetric environment around the ruthenium center. The (*R*)-MeO-BiPHEP/dmpe (dmpe = 1,2-bis(dimethylphosphino)ethane) catalyst (**10**) was found to be effective for the asymmetric alkylation of benzylic chlorides, while the (*R*)-DIFLUORPHOS/dmpe catalyst (**11**) was optimal for the nucleophilic substitution of less activated alkyl bromides; the scope of the respective catalysts was also explored.

Introduction

In recent decades the rapid growth in the field of asymmetric transition metal-catalyzed transformations has revealed the importance of chiral phosphines as ligands.[1,2] During the infancy of the field,[3] Knowles and co-workers successfully utilized P-stereogenic phosphines as ligands for rhodium in the first practical and highly enantioselective olefin hydrogenation in their synthesis of L-DOPA.[4] In spite of the early promise P-stereogenic phosphines exhibited as ligands, at present, phosphines bearing either axial or planar chirality or stereogenic carbon centers are more commonly employed; this is largely due to the lack of concise and efficient methods for the generation of phosphorus stereocenters. Traditionally, the latter molecules were obtained in enantioenriched form through resolutions or with the aid of chiral auxiliaries.[5−7] While the formation of a variety of carbon stereocenters has been effectively achieved using asymmetric catalysis, stereoselective transition metal-catalyzed approaches for the preparation of P-stereogenic phosphines have, until recently, been nonexistent.[8−10] At this time, the most developed metal-mediated process proceeds by the arylation of secondary phosphines via cross-coupling pathways;[11−19] however, P-stereogenic phosphines have also been accessed by the hydrophosphination of electron-deficient olefins[20,21] and the alkylation of chiral racemic secondary phosphines with alkyl halides.[22−24] Although we and others have demonstrated these promising new approaches for the synthesis of tertiary P-stereogenic phosphines,[25−27] the potential breadth of these reactions has yet to be fully realized. In our own efforts aimed at accomplishing this goal, we herein report details from our studies into the development of an enantioselective Ru(II)-catalyzed alkylation of phosphines.

Results and Discussion

Proposed Catalytic Cycle. On the basis of stoichiometric experiments with the achiral phosphido complex (dmpe)$_2$Ru(H)-(PMePh) (**1**) (dmpe = 1,2-bis(dimethylphosphino)ethane), the catalytic cycle for phosphine alkylation depicted in Scheme 1 was proposed.[22,28] Addition of an equivalent of methylphenylphosphine (**2**) to the coordinatively unsaturated, cationic Ru(II) intermediate (**A** in Scheme 1) gives rise to the secondary phosphine complex **B**. Coordination to the metal center causes acidification of the P−H bond, allowing alkoxide bases to quantitatively deprotonate **B** to form phosphido complex **C**. This acidification is crucial for developing an asymmetric reaction since facile deprotonation of **B** is necessary given the potential for the racemic background reaction.

Once generated, Ru(II) phosphido complex **C** can react with a variety of electrophiles[29,30] to afford tertiary phosphine ruthenium complexes (**D**).[22,28] Mechanistic studies by Glueck and co-workers on an analogous Pt(II) system showed that alkylation of the phosphido intermediate was the enantiodetermining step.[24] Since late transition metal phosphido complexes

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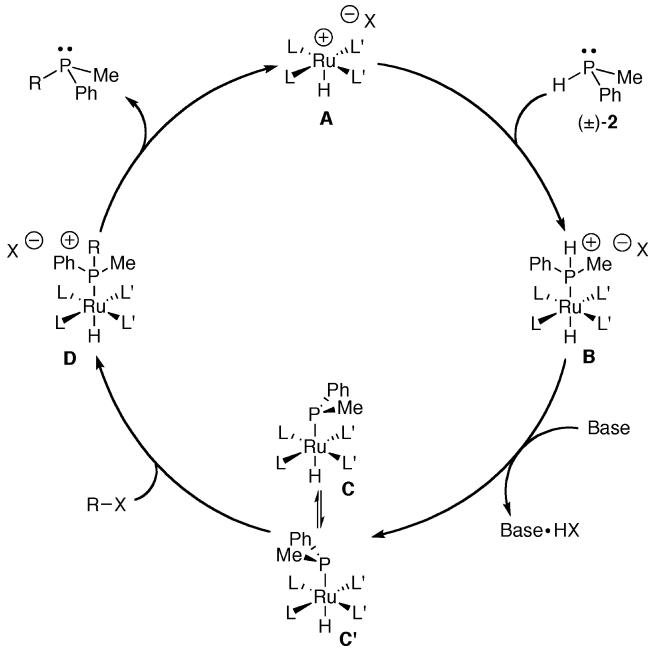
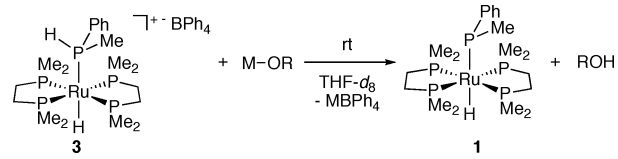
Scheme 1. Proposed Catalytic Cycle for the Ru(II) Phosphido Alkylation

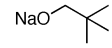
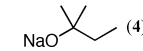


are known to have low barriers to pyramidal inversion,[31] the phosphido complex **C** will be in rapid equilibrium with its epimer **C′**. This epimerization enables a dynamic kinetic asymmetric transformation (DyKAT) to occur, whereby the racemic secondary phosphine is converted to an optically active tertiary phosphine via the enantiodetermining alkylation of the phosphido complex intermediate. In reactions with bulky electrophiles, the newly formed tertiary phosphine rapidly dissociates from the metal center to re-form **A**, but for smaller electrophiles the phosphine complexes **D** are relatively stable.[28] When rendering this transformation asymmetric, we expected the use of bulky chiral ligands to increase steric crowding around the metal center, aiding in phosphine dissociation and avoiding product inhibition.

Reaction Design. Prior to ligand optimization, we first wanted to determine the optimal base for the asymmetric alkylation. A

Table 1. Evaluation of Alkoxide Bases for Phosphide Generation[a]



entry	M-OR	soluble in THF?	product (**1**)?
1	NaOEt	no	no
2	KOEt	no	yes
3	KO^{t}Bu	no	yes
4	NaO^{i}Pr	no	no
5	NaOPh	yes	no
6		yes	yes
7	 (**4**)	yes	yes

[a] Reactions were conducted with equimolar amounts of **3** and base. Solubility was determined qualitatively. Conversion to the phosphido complex **1** was determined by ^{1}H and ^{31}P NMR spectroscopy.

significant obstacle to rendering this reaction highly enantioselective is the background reaction, where free phosphine can be deprotonated by the base and directly alkylated. To address this problem, we sought to identify a soluble base that would generate a ruthenium phosphido complex (**B** to **C** in Scheme 1) while also minimizing the background reaction. Although amides were found to competently generate the phosphido complex **1**,[22] we opted to focus on weaker alkoxide bases (Table 1).

To establish whether a base was suitable for the generation of **1**, an equivalent of secondary phosphine complex **3** was treated with a stoichiometric amount of alkoxide. Sodium and potassium ethoxide, KO*t*Bu, and NaO*i*Pr were insoluble in THF and thus unsuitable (entries 1−4). However, sodium 2,2-dimethyl-1-propoxide and sodium *tert*-amyloxide (**4**, NaO*t*Am) were both found to fulfill the solubility and basicity requirements (entries 6 and 7, respectively). Subsequent experiments that were monitored by ^{31}P NMR spectroscopy showed that quantitative alkylation of **1** with benzyl chloride could be effected with **4**, but not with the neopentyl alkoxide. Therefore, the tertiary alkoxide **4** was deemed to be the most suitable base for the catalytic phosphido alkylation.

We were wary of a possible undesired side-reaction in which sodium *tert*-amyloxide (**4**) coordinates with the cationic Ru(II)

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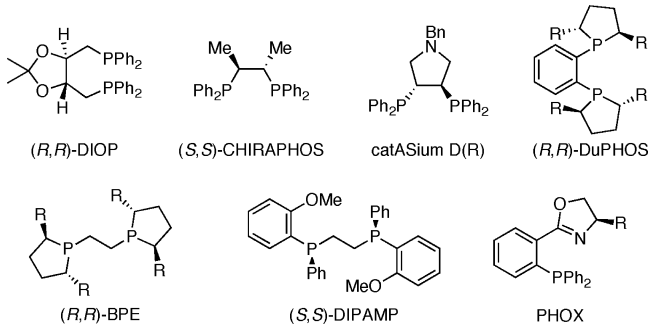


Figure 1. Chiral diphosphine ligands evaluated for the Ru(II) phosphido alkylation.

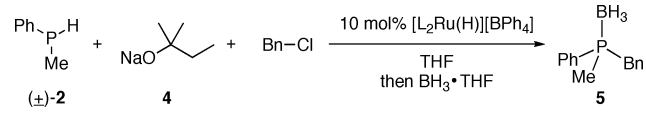
catalyst. Depending on the lability of the alkoxo ligand,[32] this ligand association could decrease the effective concentration of the catalyst in the reaction, indirectly favoring the background reaction. Pleasingly, no evidence was ever observed by either ^{1}H or ^{31}P NMR spectroscopy to suggest that a Ru-alkoxide was forming in appreciable concentrations. We suspect that the bulky alkoxide is an unsuitable ligand due to steric interactions.

Having identified the optimal base, we next set out to evaluate chiral ligands for the asymmetric alkylation. Given the high concentration of phosphine species that would be present in solution during the course of the reaction, there was a strong possibility of ligand exchange between monodentate phosphines, which could subsequently lead to an autocatalytic reaction.[15] To avoid this, we chose to focus on electron-rich bidentate phosphine ligands that would be less susceptible to displacement (Figure 1).

A variety of coordinatively unsaturated catalysts of type $[L_2Ru(H)][BPh_4]$ (where L = chiral diphosphine) were prepared in a straightforward manner from either $[(NH_2NMe_2)_3Ru(H)(cod)][BPh_4]$[33] (cod = 1,5-cyclooctadiene) or $(PPh_3)_3Ru(Cl)(H)$.[34] In preparing the chiral catalysts, higher reaction temperatures were always required, suggesting that ligand exchange was relatively slow at ambient temperatures. This observation was encouraging, as it indicated the autocatalysis resulting from ligand exchange would not be a competitive pathway.

The chiral cationic Ru(II) catalysts were then evaluated in the asymmetric alkylation. In the presence of 10 mol % catalyst, **2** was treated with a slight excess of benzyl chloride and **4** in THF; the product was then isolated as the air- and moisture-tolerant phosphine-borane adduct **5** (Table 2). The performance of the catalysts was assessed at room temperature (entries 1−12) and the enantioselectivities were found to be highly dependent on the ligand structure. When the (*R*,*R*)-Me-BPE catalyst was subjected to the alkylation reaction, tertiary phosphine **5** was isolated in 21% ee (entry 4). Anticipating that the enantioselectivity would improve by increasing the steric bulk of the phospholane, we looked at the corresponding Et-BPE catalyst, which, surprisingly, furnished **5** in a diminished 9% ee (entry 5). The P-stereogenic DIPAMP ligand was effective: phosphine-borane **5** was isolated in 56% ee (entry 8). A series of phosphinooxazoline (PHOX) ligands were examined, but did not reveal any clear steric trends (entries 9−12); however, the

Table 2. Ligand Screen for the Ru(II)-Catalyzed Phosphine Alkylation[a]



entry	ligand	time (h)	temp °C	% ee[b]
1	(*R*,*R*)-DIOP	0.3	23	0
2	(*S*,*S*)-CHIRAPHOS	3	23	8
3	catASium D(R)	2.5	23	23
4	(*R*,*R*)-Me-BPE	0.3	23	21 (18[c])
5	(*R*,*R*)-Et-BPE	0.3	23	9
6	(*R*,*R*)-Me-DuPHOS	0.3	23	10
7	(*R*,*R*)-*i*Pr-DuPHOS	0.3	23	0
8	(*S*,*S*)-DIPAMP	1.5	23	56
9	(*R*)-*i*Pr-PHOX (**6**)	2	23	30 (19[c])
10	(*R*)-Ph-PHOX	2	23	10
11	(*R*)-Me-PHOX	2	23	24
12	(*S*)-Bn-PHOX	3.5	23	7
13	catASium D(R)	68	−30	8
14	(*R*,*R*)-Me-BPE	36	−30	19
15	(*S*,*S*)-DIPAMP	66	−30	43
16	(*R*)-*i*Pr-PHOX (**6**)	60	−30	−79
17	(*S*)-*i*-Pr-PHOX (*ent*-**6**)	60	−30	75
18	(*R*)-Ph-PHOX	70	−30	9
19	(*R*)-Me-PHOX	62	−30	11
20	(*S*)-Bn-PHOX	65	−30	9

[a] Reactions were conducted with 1.2 equiv of BnCl and **4** and were quenched with 5 equiv of BH_3•THF. Quantitative conversion to product (**5**) was observed by ^{31}P NMR spectroscopy before quenching. [b] Measured by chiral HPLC. Negative sign indicates a reversal in enantioselectivity. [c] Reaction run with 2 mol % of catalyst.

*i*Pr-PHOX catalyst **6** did show initial promise, furnishing **5** in 30% ee (entry 9).

When the catalyst loading was reduced from 10 to 2 mol %, the enantioselectivity in the alkylation was also decreased. For instance, when 2 mol % of the Me-BPE catalyst was employed, benzylmethylphenylphosphine-borane **5** was isolated in 18% ee (entry 4). A more dramatic decrease in the enantioselectivity was observed when only 2 mol % of *i*Pr-PHOX catalyst **6** was used—the product **5** was isolated in only 19% ee, an 11% drop. These results at lower catalyst loadings are indicative of a competitive background reaction.

Hoping to slow the background reaction and enhance the enantioselectivity, the asymmetric alkylations were performed at reduced temperatures. Lowering the temperature to −30 °C required longer reaction times, without general improvements in the enantioselectivity. For instance, the (*S*,*S*)-DIPAMP catalyst afforded a decrease from 56% ee at room temperature to 43% ee (entry 15). However, with (*R*)-*i*Pr-PHOX catalyst **6**, an unusual reversal and improvement in enantioselectivity was observed (entry 16)—phosphine **2** was produced in 79% ee when the reaction temperature was lowered to −30 °C. This temperature dependent reversal in selectivity with catalyst **6** suggests that the enantiodetermining step is changing (vide infra).[35−38] When this benzylation was mediated by the (*S*)-*i*Pr-PHOX catalyst, phosphine-borane **5** was recovered in 75% ee (entry 17). The observation that Ru(II)-complexes **6** and *ent*-**6** produce

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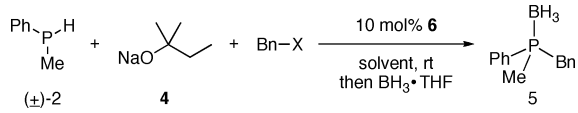
Table 3. Optimization of Reaction Variables[a]



entry	X	equiv base	solvent	% ee[b]
1	Cl	1.2	THF	30 (32[c])
2	Cl	2.5	THF	32
3	Cl	1.2	PhH[d]	0
4	Cl	1.2	PhMe[d]	3
5	Cl	1.2	dioxane[d]	5
6	Br	1.2	THF	8 (6[e])
7	OCO_2Bn	1.2	THF	—[f]

[a] Reactions were quenched with 5 equiv of BH_3•THF. Reactions were observed to proceed quantitatively by ^{31}P NMR spectroscopy. [b] Measured by chiral HPLC. [c] Reaction run with 20 mol % PPh_3. [d] Reaction solutions were heterogeneous. [e] Reaction run at −38 °C. [f] Desired product was not observed.

the opposite enantiomers indicates the product chirality is catalyst-controlled. Furthermore, autocatalysis appears unlikely as no spectroscopic evidence was observed to suggest the phosphinooxazoline was dissociating from ruthenium.

Once it was established that the *i*Pr-PHOX catalyst **6** was the best for the enantioselective phosphine alkylation, we set out to investigate several other reaction variables (Table 3). When a catalytic amount of triphenylphosphine was added to the reaction, phosphine-borane **5** was isolated in 32% ee, as compared to 30% when no additional phosphine was added (entry 1). The observation that PPh_3 does not erode the enantioselectivity indicates that product inhibition is not occurring; that is, tertiary phosphines do not out-compete the secondary phosphine for coordination to the ruthenium center.

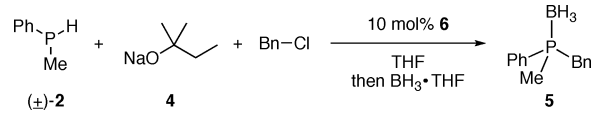
The enantioselectivity was unaffected by a higher concentration of sodium *tert*-amyloxide (entry 2). This result came as a surprise given that the background reaction was expected to be more competitive with more base, just as it was when the catalyst loading was lowered. This result also indicates that the base was not binding to the catalyst to form a Ru-alkoxide. A brief solvent screen was performed, but the solvents that could be evaluated were limited by reactivity and solubility. For instance, polar aprotic solvents like CH_2Cl_2, $CHCl_3$, and MeCN led to catalyst decomposition. Since catalyst **6** was insoluble in benzene, toluene, and dioxane, it was not unexpected that they were also poor solvents for the asymmetric alkylation. In these examples (entries 3−5), the low ee's observed are likely due to the low catalyst solubility.

The effect of the leaving group was also examined—when the more electrophilic benzyl bromide was submitted to the reaction, product **5** was isolated in only 8% ee; cooling the reaction mixture to −38 °C did not afford an improvement in the enantioselectivity (entry 6). Conversely, the less reactive dibenzylcarbonate failed to furnish the desired tertiary phosphine (entry 7). Initial studies thus show the optimal conditions for the benzylation of **2** are with *i*Pr-PHOX catalyst **6** and a slight excess of electrophile and NaO*t*Am in THF at −30 °C.

Effect of Temperature on the Operation of the *i*Pr-PHOX Catalyst (6). To study the unusual temperature dependent reversal in enantioselectivity discussed above, **2** was treated with benzyl chloride, **4**, and 10 mol % of catalyst **6** over a range of temperatures (Table 4). As a point of reference, the reaction at room temperature proceeded in 30% ee (entry 2).

When the alkylation was performed at 45 °C, phosphine-borane **5** was isolated in 12% ee (entry 1). Cooling the mixture to 0 °C also led to an apparent decrease in enantioselectivity: the alkylation proceeded in 8% ee (entry 3). Further reducing the temperature to −15 °C led to a reversal in the enantioinduction with the desired phosphine forming in 19% ee (entry 4). Alkylation of **2** with benzyl chloride at −38 °C afforded the product **5** in 80% ee (entry 6). These results show a clear trend where the sense of induction is reversed and also improved with decreasing temperature.

Table 4. Effect of Temperature on the Enantioselectivity of Alkylation with *i*Pr-PHOX Catalyst **6**[a]



entry	temp (°C)	$1/T$ (10^{-3} K^{-1})	time (h)[b]	% ee[c]	$\ln(k_S/k_r)$[d]
1	45	3.143	1.5	12	0.2412
2	23	3.377	2	30	0.6190
3	0	3.661	45	8	0.1603
4	−15	3.873	60	−19	−0.3847
5	−30	4.113	60	−79	−2.143
6	−38	4.253	107	−80	−2.197

[a] Reactions were conducted with 1.2 equiv of BnCl and **4** and were quenched with 5 equiv of BH_3•THF. Reactions proceeded to quantitative conversion as observed by ^{31}P NMR spectroscopy. [b] Unoptimized reaction times. [c] Measured by chiral HPLC. Negative sign indicates a reversal in enantioselectivity. [d] $\ln(k_s/k_r) = \ln[(100 + \%\ ee)/(100 - \%\ ee)]$.

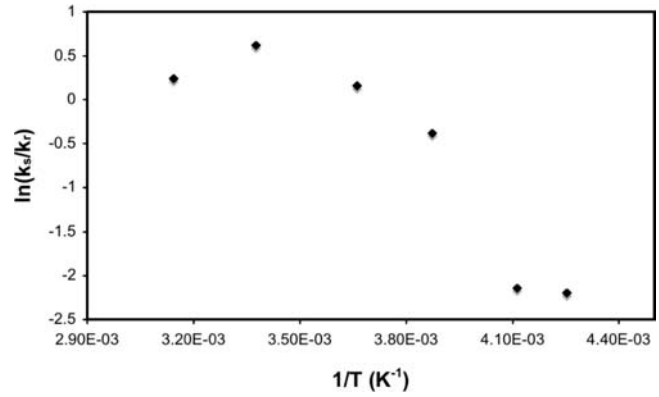


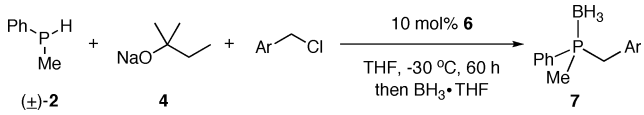
Figure 2. Correlation of temperature and enantioselectivity of the phosphine alkylation with catalyst **6** as represented by a plot of $\ln(k_S/k_R)$ vs $1/T$.

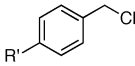
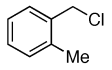
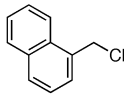
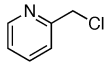
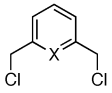
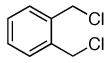
The correlation between temperature and the enantioselectivity of the alkylation catalyzed by *i*Pr-PHOX catalyst **6** is depicted in Figure 2. The ee's from the reactions are expressed as the natural logarithm of the relative rate constant for the formation of (*S*)- and (*R*)-benzylmethylphenylphosphine, $\ln(k_S/k_R)$, which is then plotted as a function of the inverse temperature ($1/T$, K^{-1}).[39] The value of $\ln(k_S/k_R)$ was calculated according to eq 1, which can also be written as the differential Eyring equation shown in eq 2.[35,38]

$$\ln\left(\frac{k_S}{k_R}\right) = \ln\left[\frac{(100 + \%\ ee)}{(100 - \%\ ee)}\right] \quad (1)$$

$$\ln\left(\frac{k_S}{k_R}\right) = \frac{-\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R} \quad (2)$$

Table 5. Enantioselective Alkylation of **2** with Benzylic Chlorides Catalyzed by *i*Pr-PHOX Catalyst **6**[a]



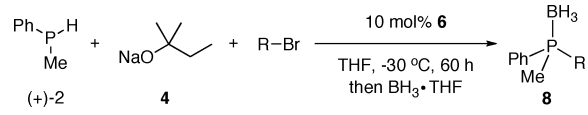
entry	$ArCH_2Cl$		product	% yield[b]	% ee[c]
1		R' = H	**5**	91	75 (92[d])
2		R' = Cl	**7a**	96	41 (33[d])
3		R' = Me	**7b**	80	83
4		R' = OMe	**7c**	85	85
5			**7d**	92	57
6			**7e**	96	59
7			**7f**	94	48
8			**7g**	80	68
9		X = CH	**7h**	86	95[e]
10		X = N	**7i**	89	84[f]
11			**7j**	87	74[g]

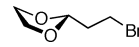
[a] Reactions were conducted with 1.2 equiv of electrophile and **4** and quenched with 5 equiv of BH_3·THF. [b] Isolated yields. [c] Measured by chiral HPLC. [d] The % ee after a single recrystallization from ethanol. [e] A 74:26 C_2/meso dr determined by HPLC. [f] C_2/meso ratio of 58:42. [g] A 33:67 mixture of C_2/meso.

If the mechanism of enantioselection were constant over a wide temperature range, a linear plot would be expected because $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ should remain unchanged. Conversely, if the enantiodetermining step is changing at different temperatures, the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values will likewise vary, giving a nonlinear curve. Since the plot of $\ln(k_S/k_R)$ vs $1/T$ shown in Figure 2 is nonlinear, it can be inferred that the enantiodetermining step is changing over the range of temperatures examined. Thus, the observed reversal in absolute induction could arise from a temperature-dependent interchange of the enantiodetermining mechanisms. In situ ^{1}H NMR spectroscopy experiments aimed at observing the ruthenium phosphido intermediates of complex **6** led to the observation of a multitude of hydride signals. This suggests that a mechanism more convoluted than depicted in Scheme 1 may be operative.

Scope of the [(*i*Pr-PHOX)$_2$Ru(H)] (6) Catalyzed Reactions. We next explored the scope of the reaction under the optimal conditions identified earlier. The asymmetric alkylation was effective for the reaction with a variety of benzylic chlorides (Table 5).[22] The reaction of **2** with benzyl chloride was repeated, and benzylmethylphenylphosphine-borane **5** was isolated in 75% ee; however, a single recrystallization of the product gave further enrichment to 92% ee (entry 1). The alkylation of 4-chlorobenzyl chloride proceeded efficiently (96% yield), but the electron-deficient substrate furnished **7a** in only 41% ee (entry 2). Reactions with 4-methyl- and 4-methoxybenzyl chlorides were

Table 6. Enantioselective Alkylation of **2** with Aliphatic Bromides Catalyzed by *i*Pr-PHOX Catalyst **6**[a]



entry	R–Br	product	% yield[b]	% ee[c]
1		**8a**	70	57
2		**8b**	76	5
3		--	nd[d]	--
4		--	nd[e]	--

[a] Reactions were conducted with 1.2 equiv of electrophile and **4** and quenched with 5 equiv of BH_3·THF. [b] Isolated yields. [c] Measured by chiral HPLC. [d] Measured <31% conversion after 48 h. [e] Observed 50% conversion after 40 h with no alkyl bromide remaining.

equally efficient but much more selective: phosphine-boranes **7b** and **7c**were isolated in 83% and 85% ee, respectively (entries 3 and 4). Substrates with substitution in the ortho position reacted well, although with lower selectivities (entries 5 and 6).

Heteroaryl substrates were also tolerated (entries 7 and 8)—pyridyl- (48% ee) and furyl-containing (68% ee) phosphines that could potentially be used as hemilabile bidentate ligands were synthesized. Chelating diphosphines were also prepared efficiently with good enantioselectivities from the double substitutions (entries 9−11).[40] While a P-chiral pincer ligand **7h** was isolated in 95% ee (entry 9), the corresponding PNP pincer ligand **7i** was furnished in 84% ee (entry 10). The diphosphine **7j** resulting from the double alkylation of 1,2-bis(chloromethyl)benzene was recovered in 74% ee (entry 11), consistent with earlier observations that ortho substitution lowered the enantioselectivity.

We next looked to diversify the scope of the asymmetric alkylation with nonbenzylic electrophiles (Table 6). Phosphine **2** reacted efficiently with ethyl bromide to furnish phosphine-borane **8a** in 57% ee (entry 1). Although bromo(trimethylsilyl)methane was suitably reactive, the product phosphine-borane **8b** was isolated in only 5% ee (entry 2). The more sterically encumbered (bromomethyl)cyclohexane afforded only 30% conversion to product after 2 days at −30 °C, and extended reaction times did not lead to greater product formation (entry 3). When **2** was treated with 2-(2-bromoethyl)-1,3-dioxolane at −30 °C, only 50% conversion to product was observed (entry 4). Although unreacted phosphine remained, the alkyl bromide had been completely consumed by partial alkylation and competitive HBr elimination.

While the *i*Pr-PHOX catalyst **6** was effective for phosphine alkylation with benzylic chlorides, it showed very limited scope with unactivated aliphatic bromides. These results demonstrated a need for more active catalysts that would also be highly selective for nucleophilic substitution.

Development of Second-Generation Catalysts. In seeking to improve the catalysts, our primary objective was to identify ruthenium complexes that would effect the desired substitution at room temperature with useful levels of enantioselectivity and

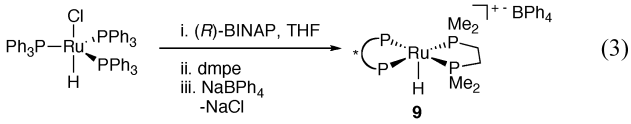
(39) Since the absolute configuration of the phosphine-borane **5** has not yet been established, the k_S and k_R designations are arbitrary.

(40) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1994**, 99–100.

also generate a phosphido species capable of alkylating benzylic electrophiles, as well as less reactive alkyl halides. During the initial ligand screen (Table 2), we observed a dramatic decrease in ee when the *i*Pr-PHOX catalyst loading was reduced from 10 to 2 mol % (entry 9); however, a nearly negligible drop was measured for the Me-BPE catalyst (21% to 18% ee, entry 4). These observations suggested that the tetraphosphine Ru(II) phosphido species was more reactive than the corresponding P,N,N,P-complex at ambient temperatures. Thus, we opted to focus our efforts on tetraphosphine complexes.

While considering other catalysts, we were immediately drawn to the octahedral chiral mixed-ligand ruthenium(II) diamine/diphosphine complexes developed by Noyori for asymmetric transfer hydrogenations.[41−44] Since our phosphine alkylation also utilizes ligand-centered (as opposed to metal-centered) reactivity, we thought analogous Ru−tetraphosphine complexes would be a good starting point. Moreover, the discovery of ruthenium catalysts supported by achiral tropos diphosphines and asymmetric diamines by the Mikami group[45,46] led us to believe the pairing of chiral and achiral diphosphines could potentially furnish an effective catalyst for the desired enantioselective phosphine alkylation.

In order to establish proof-of-principle, the coordinatively unsaturated [((*R*)-BINAP)(dmpe)Ru(H)][BPh_4] complex **9** was synthesized in a straightforward manner from $(PPh_3)_3Ru(Cl)(H)$ (eq 3).[34] The sequential addition of BINAP, followed by dmpe, allowed for the introduction of two distinct ligands. Abstraction of the chloride with sodium tetraphenylborate furnished the cationic species with the desired vacant coordination site.

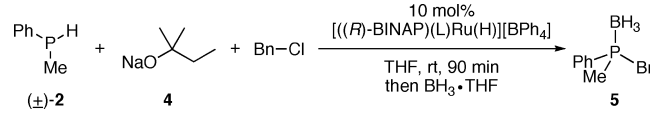


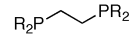
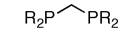
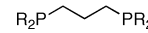
(3)

When 10 mol % of BINAP/dmpe catalyst **9** was subjected to the reaction of **2** with benzyl chloride, the tertiary phosphine-borane **5** was isolated in 49% ee (Table 7, entry 1). This observation indicates that a single chiral ligand was sufficient to create an effective asymmetric environment for the octahedral Ru−phosphido complex. Additionally, given Mikami's observations,[45,46] it is feasible that BINAP is relaying its stereochemical information to the dmpe ligand and causing it to adopt a chiral geometry. On the basis of this result, a variety of BINAP mixed-ligand catalysts were prepared to evaluate which achiral ligand would be best suited for the alkylation (Table 7).

The BINAP/dmpe catalyst **9** also effected the alkylation at −30 °C, affording only a modest increase to 53% ee (entry 1). When 1,2-bis(diethylphosphino)ethane (depe) was employed as the co-ligand, the enantioselectivity decreased to 19% ee (entry 2). Further increasing the steric bulk of the P-substituents

Table 7. Evaluation of Achiral Co-ligands in the Benzylation of **2** with BINAP Mixed-Ligand Catalysts[a]



entry	ligand (L)		% ee[b]
1		R = Me (**9**)	49 (53[c])
2		R = Et	19
3		R = Cy	0
4		R = Ph	0
5		R = Me	38 (8[c])
6		R = Cy	0
7		R = Ph	2
8		R = Cy	0
9		R = Ph	0

[a] Reactions were conducted with 1.25 equiv of BnCl and **4** and then quenched with 5 equiv of BH_3•THF. Quantitative alkylation was observed by ^{31}P NMR spectroscopy. Isolated yields were not determined. [b] Measured by chiral HPLC. [c] Reaction was performed at −30 °C.

furnished only racemic **5** in the alkylations (entries 3 and 4). The dependence of the enantioselectivity on the tether length of the achiral diphosphine was very specific: changing from dmpe to the methylene-bridged 1,2-bis(dimethylphosphino)methane (dmpm) led to the formation of **5** in only 38% ee (entry 5). In analogy to the dmpe series, larger P-substituents rendered the catalyst unselective (entries 6 and 7). Lengthening the diphosphine backbone to a propyl tether also resulted in the formation of unsuitable catalysts (entries 8 and 9). From these results it is apparent that the enantioselectivity of the alkylation is not dictated solely by BINAP, demonstrating the importance of the achiral ligand in establishing an asymmetric environment around the ruthenium center.

Having ascertained that dmpe was the optimal achiral diphosphine for the asymmetric alkylation, we next evaluated a variety of chiral phosphine ligands (Figure 3). We chose to focus on atropisomeric diphosphines, as they have been shown to be effective ligands for ruthenium.[47,48] The mixed-ligand Ru(II) catalysts were prepared with atropos biaryl diphosphines and dmpe from $(PPh_3)_3Ru(Cl)(H)$ as described in eq 3.

With the hope of identifying a catalyst that was suitable for the asymmetric alkylation with benzylic and nonbenzylic substrates, both types of electrophile were evaluated in the ligand optimization (Table 8). The enantioselectivities observed in these studies revealed subtle stereoelectronic trends. As the BINAP and SEGPHOS series show, increasing the steric bulk of the catalyst led to a loss of selectivity in the alkylation of **2** with benzylic chlorides, but this was not a significant factor in the reactions with alkyl bromides (entries 1−5). The MeO- and Cl-MeO-BiPHEP/dmpe catalysts suggested perhaps electron-deficient ligands may be less suitable for the reaction with benzylic electrophiles, but a better fit for the alkylation of aliphatic substrates (entries 6 and 7); this trend was supported by the performance of the DIFLUORPHOS/dmpe catalyst (**11**).

Although a single mixed-ligand catalyst that could effectively mediate the asymmetric alkylation with both benzylic and

(41) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703–1707.
(42) Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 1086–1087.
(43) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530.
(44) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510–6511.
(45) Aikawa, K.; Mikami, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5455–5458.
(46) Mikami, K.; Wakabayashi, K.; Aikawa, K. *Org. Lett.* **2006**, *8*, 1517–1519.
(47) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264–267.
(48) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320–325.

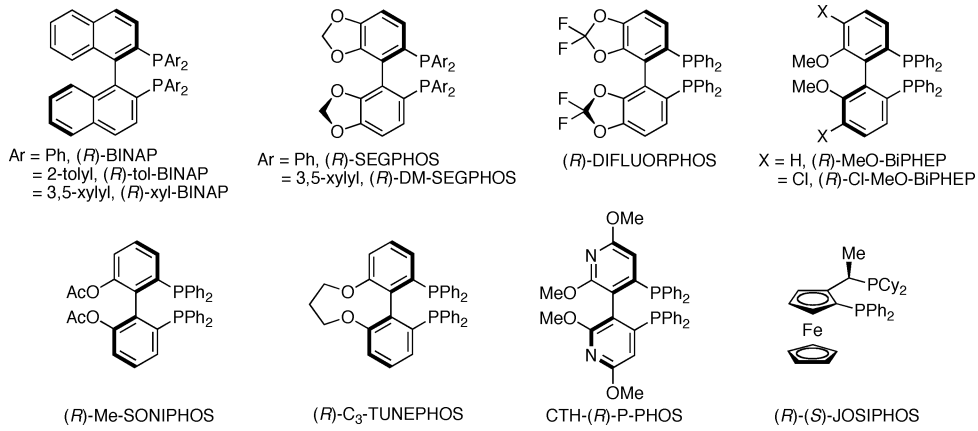
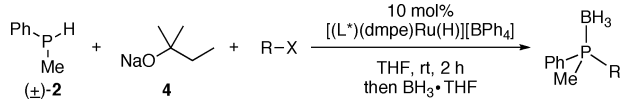
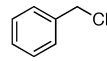
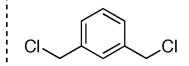
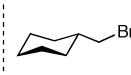


Figure 3. Chiral ligands evaluated for the mixed-ligand Ru(II) catalysts.

Table 8. Optimization of the Chiral Mixed-Ligand Catalysts[a]



entry	chiral ligand (L*)				
		% ee[b]			
1	(*R*)-BINAP (**9**)	49	75 (62:38 dr)	21	32
2	(*R*)-tol-BINAP	55	87 (67:33 dr)	27	37
3	(*R*)-xyl-BINAP	9	--	36	--
4	(*R*)-SEGPHOS	58	86 (64:36 dr)	49	37
5	(*R*)-DM-SEGPHOS	10	36 (50:50 dr)	52	30
6	(*R*)-MeO-BiPHEP (**10**)	68	87 (65:35 dr)	28	25
7	(*R*)-Cl-MeO-BiPHEP	59	75 (61:39 dr)	56	50
8	(*R*)-DIFLUORPHOS (**11**)	49	83 (63:37 dr)	66	45
9	(*R*)-C_3-TUNEPHOS	27	--	18	--
10	(*R*)-Me-SONIPHOS	21	--	27	--
11	CTH-(*R*)-P-PHOS	54	--	39	--
12	(*R*)-(*S*)-JOSIPHOS	26	--	7	--

[a] Reactions were conducted with 1.2 equiv of electrophile (only 0.51 equiv of 1,3-bis(chloromethyl)benzene) and 1.2 equiv of **4** and then quenched with 5 equiv of BH_3•THF. Quantitative alkylation was observed by ^{31}P NMR spectroscopy. [b] Measured by chiral HPLC. Diastereomeric mixture (C_2/meso) measured by HPLC.

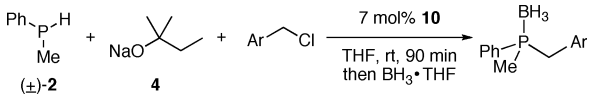
aliphatic electrophiles was not identified, we were able to prepare two complementary catalysts to accomplish these tasks. Whereas reactions with the *i*Pr-PHOX catalyst **6** had to be performed at −30 °C to achieve useful enantioselectivities, both of the mixed-ligand catalysts, **10** and **11**, were effective at room temperature (Table 8). While the MeO-BIPHEP/dmpe catalyst **10** effected the alkylation with benzylic chlorides (entry 6), DIFLUORPHOS/dmpe complex **11** was clearly superior for the substitutions with the less activated alkyl bromides (entry 8). Additionally, ^{31}P NMR spectroscopic evidence suggests the dmpe ligands are adopting a chiral conformation: the NMR spectrum of **11** shows four distinct multiplets, indicating each phosphorus atom is in a unique stereochemical environment.

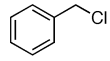
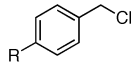
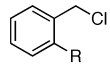
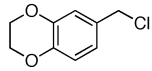
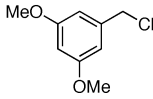
Scope of the [(MeO-BiPHEP)(dmpe)Ru(H)] (10)-Catalyzed Reactions. In expanding the scope of the benzylation, we found that the catalyst loading could be reduced to 7 mol % without affecting the enantioselectivity or the reaction efficiency (Table 9). The reaction of secondary phosphine **2** with benzyl chloride proceeded quantitatively and furnished the phosphine-borane **5** in 68% ee (entry 1) as previously observed. In this case, lowering the reaction temperature to −30 °C yielded a modest increase to 75% ee; however, this improvement did not prove to be a general phenomenon afforded to all substrates.

As was observed with *i*Pr-PHOX catalyst **6**, the alkylation of electron-poor electrophiles was less enantioselective. While the reaction of 4-chlorobenzyl chloride proceeded in 45% ee (entry 2), the electron-releasing 4-methoxy substrate yielded phosphine-borane **7c** in 61% ee and 97% yield (entry 3). A similar trend was observed for the ortho-substituted benzyl chlorides (entries 4−6); although the enantioselectivities were impacted, the reactions were still observed to proceed with quantitative consumption of the phosphine. It should be noted that the mixed-ligand catalyst was not as affected by the ortho-substitution as the *i*Pr-PHOX catalyst. Other electron-rich substrates proceeded with moderate enantioselectivity: the 1,4-benzodioxane-containing phosphine (**12c**, entry 7) was isolated in 62% ee and 90% yield, while (3,5-dimethoxybenzyl)methylphenylphosphine-borane (**12d**) was recovered in 64% ee and 98% isolated yield (entry 8).

The MeO-BiPHEP/dmpe catalyst **10** was also effective for the reaction of phosphine **2** with benzylic dichlorides (Table 10). The double alkylation of 1,3-bis(chloromethyl)benzene

Table 9. Alkylation of **2** with Benzylic Chlorides Catalyzed by Mixed-Ligand MeO-BiPHEP/dmpe Catalyst **10**[a]



entry	$ArCH_2Cl$		product	% yield[b]	% ee[c]
1			**5**	92	68 (75[d])
2		R = Cl	**7a**	97	45
3		R = OMe	**7c**	96	61
4		R = Me	**7d**	--	56
5		R = Cl	**12a**	89	32
6		R = OMe	**12b**	79	56[d]
7			**12c**	90	62[d]
8			**12d**	98	64[d]

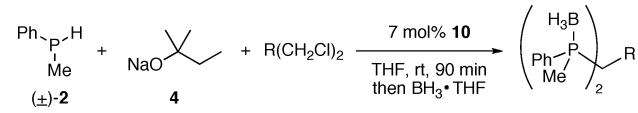
[a] Reactions were conducted with 1.2 equiv of electrophile and **4** and then quenched with 5 equiv of BH_3•THF. [b] Isolated yields. [c] Measured by chiral HPLC. Values in parentheses are the values observed from the reaction at −30 °C. [d] Enantiomeric excess is the average of two runs.

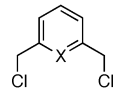
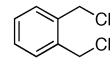
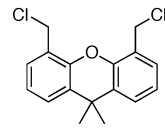
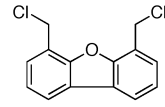
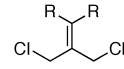
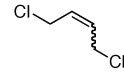
affords the PCP-pincer diphosphine **7h** in 87% ee and 87% yield, which improved to 93% ee when the reaction was run at −30 °C (entry 1). Similarly to the *i*Pr-PHOX catalyst **6**, the heteroaryl 2,6-bis(chloromethyl)pyridine was not as efficient: the diphosphine **7i** was recovered quantitatively in 76% ee (entry 2). When 1,2-bis(chloromethyl)benzene was subjected to the reaction, the product **7j** was afforded in 96% ee and 96% yield (entry 3). Of particular note, the presence of the ortho substituent does not decrease the ee as had been previously observed, suggesting the phosphine in the monoalkylated intermediate may be influencing the enantioselectivity of the second alkylation. A P-stereogenic benzylic Xantphos[49] derivative **13a** was prepared with good yield and enantioselectivity at room temperature (83% ee, entry 4), but this improved to 87% ee when the reaction temperature was reduced to −30 °C. Although structurally similar to the tricyclic xanthene, when 4,6-bis(chloromethyl)dibenzofuran substrate was treated with phosphine **2**, diphosphine **13** was obtained in only 64% ee (entry 5).

Allylic chlorides also proved to be viable electrophiles for this asymmetric phosphine alkylation (entries 6−9). For instance, when 1-chloro-2-chloromethyl-3-methyl-2-butene was subjected to the reaction, the corresponding diphosphine **13c** was isolated quantitatively in 80% ee (entry 6). The allylic phosphines were isolated as the corresponding phosphine sulfides rather than the borane-adducts to avoid hydroboration during the protection. Reducing the steric bulk of the electrophile proved beneficial as 3-chloro-2-chloromethyl-1-butene reacted to furnish **13d** in quantitative yield and 92% ee (entry 7). Since 1,2-bis(chloromethyl)benzene proceeded so efficiently, we were surprised when (*Z*)-1,4-dichloro-2-butene reacted to afford **13e** in only 60% ee (entry 8). However, consistent with the steric trend observed, the less congested (*E*)-isomer reacted to yield **13f** with an improved 77% ee and 80% yield (entry 9).

These results demonstrate the marked similarity between this mixed ligand MeO-BiPHEP/dmpe catalyst (**10**) and the *i*Pr-PHOX catalyst (**6**). However, the tetraphosphine catalyst offers the advantage of providing comparable enantioselectivity in the alkylation of activated electrophiles under much more general conditions (1.5 h at 23 °C vs 60 h at −30 °C).

Table 10. Asymmetric Alkylation of **2** with Benzylic/Allylic Dichlorides Catalyzed by MeO-BiPHEP/dmpe Catalyst **10**[a]



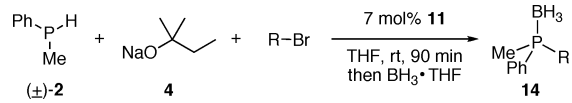
entry	$R(CH_2Cl)_2$		product	% yield[b]	C_2 : *meso*[c]	% ee[c]
1		X = CH	**7h**	87	65:35	87
				--	(69:31)	(93)
2		X = N	**7i**	99	64:36	76
3			**7j**	96	62:38	96
4			**13a**	99	66:34	83[d]
				--	(68:32)	(87)
5			**13b**	>99	58:42	64[d]
6		R = Me	**13c**	>99[e]	63:37	80
7		R = H	**13d**	>99[e]	55:45	92
8		(*Z*)	**13e**	81[e]	55:45	60
9		(*E*)	**13f**	80[e]	49:51	77

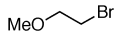
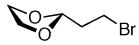
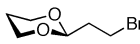
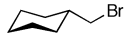
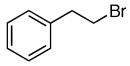
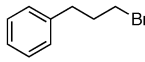
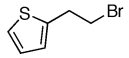
[a] Reactions were conducted with 1.0 equiv of **2**, 0.51 equiv of electrophile, and 1.2 equiv of **4** and then quenched with 5 equiv of BH_3•THF. [b] Isolated yields. [c] Measured by chiral HPLC. Values in parentheses are from reactions run at −30 °C. [d] Enantiomeric excess the average of two runs. [e] Product isolated as the phosphine sulfide.

Scope of the [(DIFLUORPHOS)(dmpe)Ru(H)] (11)-Catalyzed Reactions. The nucleophilic substitution of alkyl bromides was evaluated using DIFLUORPHOS/dmpe catalyst **11** (Table 11). Treatment of methylphenylphosphine with bromoethane, **4**, and 7 mol % **11** furnished ethylmethylphenylphosphine borane (**8a**) in 66% ee and 97% yield (entry 1). The high isolated yield of the tertiary phosphine clearly demonstrates the catalyst's preference for substitution over elimination under the reaction conditions. When 1-bromo-2-methoxyethane was subjected to the alkylation, phosphine-borane **14a** was recovered in good yield and 68% ee (entry 2). Catalyst **11** effected the quantitative alkylation of 2-(2-bromoethyl)-1,3-dioxolane in 71% ee (entry 3), but curiously, the 1,3-dioxane analog **14c** was furnished in only 57% ee (entry 4). This decrease in enantioselectivity was unexpected given the stereoelectronic similarities of the respective acetals. Consistent with results observed for the alkylation of allylic dichlorides with catalyst **10**, the bulky (bromomethyl)cyclohexane proceeded in only 45% ee and 77% yield under the action of catalyst **11** (entry 5). The DIFLUORPHOS/dmpe catalyst mediated the alkylation of phenethyl bromide in only 35% yield and 68% ee (entry 6); as a testament to the enhanced nucleophilicity of the Ru−phosphido species, only HBr elimination to form styrene was observed in the absence of catalyst. Elimination could be avoided altogether by extending the length of the alkyl chain: 1-bromo-3-phenylpropane furnished tertiary

(49) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895–904.

Table 11. Asymmetric Reaction of **2** with Alkyl Bromides Catalyzed by DIFLUORPHOS/dmpe Catalyst **11**[a]



entry	R–Br	product	% yield[b]	% ee[c]
1		**8a**	97	66[d]
2		**14a**	88	68[d]
3		**14b**	84	71
4		**14c**	82	57
5		**14d**	77	45[d]
6		**14e**	35	68
7		**14f**	91	72
8		**14g**	84	69

[a] Reactions were conducted with 1.2 equiv of electrophile and **4** and then quenched with 5 equiv of BH_3•THF. [b] Isolated yields. [c] Measured by chiral HPLC. [d] Enantiomeric excess the average of two runs.

phosphine **14f** in 72% ee and 91% yield (entry 7). The potential hemilabile P,S-bidentate ligand **14g** was prepared in 69% ee and 84% yield from 2-(2-bromomethyl)thiophene (entry 8).

While DIFLUORPHOS/dmpe catalyst **11** was effective for the reaction of phosphine **2** with simple aliphatic electrophiles, we were especially intrigued by the possibility of catalyzing the corresponding double alkylation with dibromides. Few methods for the preparation of alkyl tethered P-stereogenic diphosphines exist, and each is fairly limited. Evans and co-workers showed that C_2-symmetric diphosphines could be prepared via an enantioselective deprotonation and oxidative C−C coupling;[50] however, because the C−H deprotonation occurs adjacent to the phosphorus atom, this method is limited primarily to the formation of ethyl-bridged diphosphines. More recently, Glueck and co-workers were able to synthesize these molecules through the double alkylation of secondary diphosphines.[23,51] Although efficient, this transformation requires the preparation of the tethered phosphines. Therefore, to accomplish this goal would be to realize a direct and ideal synthesis of these potential ligands (Table 12).

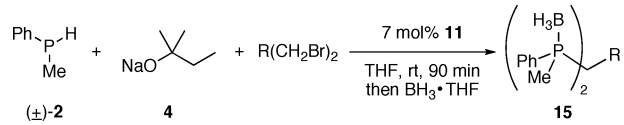
We were pleased to observe that treatment of 1,4-dibromobutane with **2** and catalyst **11** led to the formation of the P-stereogenic diphosphine **15a** in 73% ee and 95% yield (entry 1).[52] The reaction of **2** with 1,5-dibromo-3,3-dimethylpentane under the catalytic conditions afforded **15b** in 84% ee (entry 2). Notably, the asymmetric alkylation of 2,2-bis(2-bromoethyl)-

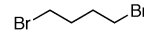
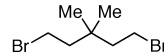
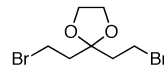
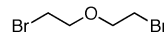
(50) Muci, A.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075–9076.

(51) Anderson, B. J.; Glueck, D. S.; DiPasquale, A. G.; Rheingold, A. L. *Organometallics* **2008**, *27*, 4992–5001.

(52) Use of shorter chain dibromides such as 1,2-dibromoethane and 1,3-dibromopropane in the asymmetric alkylation resulted primarily in HBr elimination mediated by **4**.

Table 12. Enantioselective Alkylation of **2** with Aliphatic Dibromides Catalyzed by DIFLUORPHOS/dmpe Catalyst **11**[a]



entry	$R(CH_2Br)_2$	product	% yield[b]	C_2 : *meso*[c]	% ee[c]
1		**15a**	95	74:26	73
2		**15b**	54	71:29	84
3		**15c**	58	82:18	97
4		**15d**	>99	68:32	94

[a] Reactions were conducted with 1.0 equiv of **2**, 0.51 equiv of electrophile, and 1.2 equiv of **4** and then quenched with 5 equiv of BH_3•THF. [b] Isolated yields. [c] Measured by chiral HPLC.

1,3-dioxolane furnished the corresponding diphosphine **15c** in 97% ee (entry 3). Heteroatoms could also be incorporated into the backbone: double substitution of bis(2-bromoethyl)ether yielded diphosphine **15d** quantitatively in 94% ee (entry 4). It should be noted that autocatalysis resulting from product phosphine exchange was unlikely, given that evidence of DIFLUORPHOS or dmpe dissociation was not observed spectroscopically.

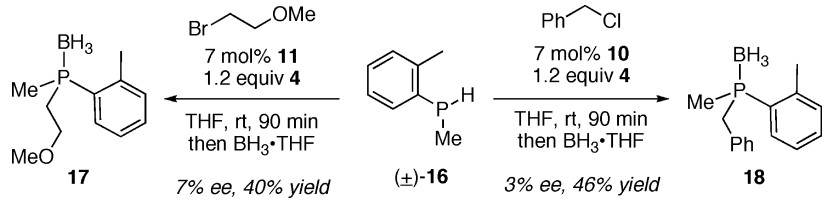
Phosphine Scope of the Mixed-Ligand Catalysts. Having demonstrated the efficacy of methylphenylphosphine as a nucleophile in the asymmetric alkylation, we next turned to examine the phosphine scope of the reaction. In the hopes of improving the stereodifferentiation in the alkylation step, larger aryl groups were introduced onto the phosphine. When methyl(2-tolyl)phosphine (**16**) was subjected to the asymmetric reaction with either mixed-ligand catalyst, the alkylation became extremely inefficient (Scheme 2). The increased steric bulk proximal to the phosphorus atom led to low reactivity and poor enantioselectivity. We hypothesize that the tolyl group not only prohibits nucleophilic attack on the electrophiles, but that it also disrupts the synergistic interaction of the chiral ligand and dmpe.

Methyl(3,5-xylyl)phosphine (**19**) was also prepared and subjected to the asymmetric phosphine alkylation (Table 13). Treatment of **19** with benzyl chloride under the optimal conditions with MeO-BiPHEP/dmpe ligand **10** afforded the tertiary phosphine-borane **20a** in 56% ee and 89% yield (entry 1), results which are comparable to methylphenylphosphine (entry 1, Table 9). When the double alkylation of 1,3-bis(chloromethyl)benzene by secondary phosphine **19** was promoted by catalyst **10**, the product diphosphine **20b** was recovered in 91% ee, 9:1 C_2/meso diastereomeric mixture and 88% yield (entry 2).

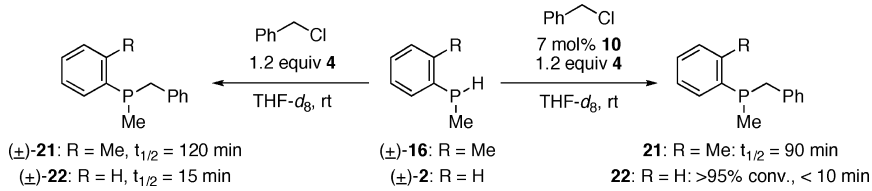
The DIFLUORPHOS/dmpe catalyst **11** was also effective for the alkylation of methyl(3,5-xylyl)phosphine. When **19** was treated with bromoethyl methyl ether, the corresponding phosphine-borane was isolated in 66% ee and 80% yield. The bulkier secondary phosphine was also effective for the reaction with alkyl dibromides: 2,2-bis(2-bromoethyl)-1,3-dioxolane reacted with **19** to afford the desired diphosphine **20d** in 92% ee, 74:26 dr (C_2/meso) and 52% yield (entry 4).

Preliminary Mechanistic Studies. Detailed mechanistic studies on this overall transformation are complicated by the fact that

Scheme 2. Attempted Asymmetric Alkylations of Methyl(2-tolyl)phosphine



Scheme 3. Half-Life Measurements for Background and Ru-Catalyzed Reactions



Scheme 4. Synthesis of Ruthenium Phosphine and Phosphido Complexes

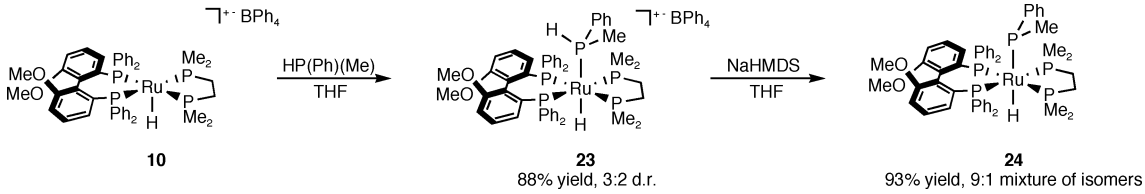
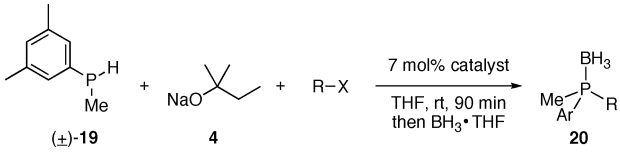
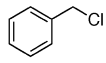
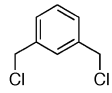
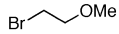
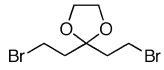


Table 13. Asymmetric Reaction of Methyl(3,5-xylyl)phosphine with the Optimal Mixed-Ligand Catalysts[a]



entry	catalyst	R-X	product	% yield[b]	% ee[c]
1	**10**		**20a**	89	56
2	**10**		**20b**	88	91[d]
3	**11**		**20c**	80	66
4	**11**		**20d**	52	92[e]

[a] Reactions were conducted with 1.2 equiv of electrophile and **4** and then quenched with 5 equiv of BH_3•THF. In the case of the dihalides, only 0.51 equiv of electrophile was used. [b] Isolated yields. [c] Measured by chiral HPLC. [d] Measured the C_2/meso ratio to be 90:10. [e] A C_2/meso ratio of 74:26 was measured.

the enantioselective ruthenium-catalyzed phosphido alkylation reaction competes with the racemic base-promoted background reaction. However, we have performed preliminary studies on the degree to which the background reaction competes with the Ru-catalyzed reaction and have also observed Ru(II) complexes that appear to be intermediates on the proposed catalytic cycle.

When we monitored the uncatalyzed and Ru-catalyzed benzylation reactions of methylphenylphosphine **2** by ^{1}H and ^{31}P NMR spectroscopy, the half-life ($t_{1/2}$) of the background reaction was measured to be 15 min, while the catalytic reaction showed complete conversion (~14 turnovers) to tertiary phosphine **22** within 10 min (Scheme 3). These dramatic rate differences clearly demonstrate the enhanced nucleophilicity observed for the ruthenium phosphido complex compared to that which is characteristic of ordinary charge-neutral phosphines.

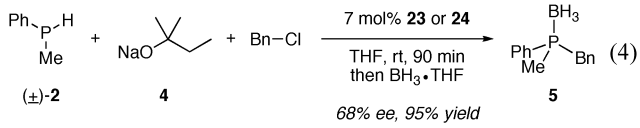
We then investigated the analogous reactions of **16** with benzyl chloride (Scheme 3). We hypothesized the low enantioselectivities observed in the alkylations of **16** were in part due to the competing background reactions (see Scheme 2). The background reaction had a $t_{1/2} = 120$ min, while the half-life of the Ru-catalyzed reaction was 90 min; both reactions proceeded to completion within 24 h at 23 °C. On the basis of these results, it appears that the increased steric bulk of methyl(2-tolyl)phosphine significantly slows the Ru-catalyzed reactions such that the background reaction becomes competitive, thus contributing to the erosion of the enantioselectivity of the overall reaction.

Focusing on the ruthenium-catalyzed reaction, stoichiometric studies were undertaken to identify putative intermediates on the catalytic cycle and to better understand the stereoselectivity of each step in the cycle. The cationic (*R*)-MeO-BIPHEP/dmpe complex **10** was treated with an equivalent of **2**, yielding cationic methylphenylphosphine complex **23** as a 3:2 mixture of diastereomers (Scheme 4). Subsequent deprotonation of complex **23** with NaHMDS afforded the phosphido complex **24** as a mixture of isomers in a 9:1 ratio (Scheme 4).[53]

Furthermore, when subjected to the reaction of benzyl chloride with methylphenylphosphine, complexes **23** and **24** were found to be catalytically competent (eq 4): in both cases benzylated product **5** was obtained in 68% ee and 95% yield, which agrees with the result obtained using catalyst **10** (see Table 9). Interestingly, the 9:1 ratio of the phosphido nucleophile is not preserved in the alkylation; that is, the formation of the tertiary phosphine is not a stereospecific process, suggesting

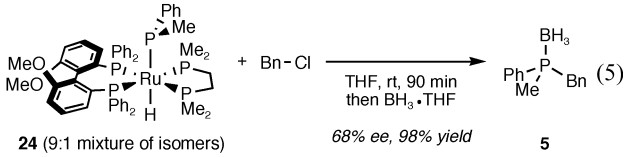
(53) Studies to identify the exact nature of the observed isomers of the phosphido species **24** are currently underway.

the P-stereocenter of the phosphido intermediate is dynamic and rapidly epimerizing. These preliminary results are consistent with the mechanistic hypothesis illustrated in Scheme 1.



(4)

The stoichiometric reaction between the diastereomeric mixture of phosphido complex **24** and benzyl chloride yielded tertiary phosphine-borane **5** in 98% yield and 68% ee (eq 5), where the major enantiomer of product obtained from the stoichiometric reaction matched that from the Ru-catalyzed alkylation. Given the absence of free phosphine and **4** in this experiment, the deleterious background reaction can be ruled out as a cause for the moderate enantioselectivity. Assuming that the phosphine alkylation is a dynamic kinetic asymmetric transformation, this result suggests that the rate of alkylation of the phosphido diastereomer which yields the minor enantiomer is competitive with the rate of reaction of the "major" diastereomer.



(5)

Conclusion

On the basis of stoichiometric experiments with the phosphido complex **1**, an enantioselective phosphine alkylation was developed. The chiral transformation relies on the rapid epimerization of a transient phosphido intermediate, which allows for a dynamic kinetic asymmetric alkylation of racemic secondary phosphines to afford enantioenriched tertiary phosphines. Initial studies showed that **6** was the optimal catalyst for this transformation. This catalyst exhibited an unusual temperature dependence in which the enantioinduction was reversed when the reaction temperature was lowered from 23 to −30 °C. A nonlinear correlation between $\ln(k_S/k_R)$ and $1/T$ suggested that the mechanism of enantioselection was changing as a function of temperature, giving rise to the observed reversal in induction. The scope of catalyst **6** was explored and limited to the alkylation of benzylic chlorides, suggesting the need for improved catalysts.

Efforts aimed at developing more reactive and selective catalysts for the alkylation led to the discovery of tetraphosphine mixed ligand catalysts. The MeO-BiPHEP/dmpe catalyst **10** which was effective for the alkylation of benzylic chlorides, performed comparably to the *i*Pr-PHOX catalyst **6**, but under ambient conditions. The discovery of the DIFLUORPHOS/dmpe catalyst **11** allowed the asymmetric phosphine alkylation to be performed with aliphatic bromides. The scope of this reaction was also extended to the preparation of alkyl-tethered P-stereogenic diphosphines. These results with catalyst **11** constitute a significant advancement of the reaction scope as previous reports were almost exclusively limited to the alkylation of benzylic electrophiles.[22,23] More importantly, the success of these mixed-ligand catalysts demonstrates the concept of a chiral ligand relaying stereochemical information to an achiral ligand, which in turn adopts a chiral conformation. The synergistic interaction of the two ligands represents an under-utilized, yet effective method of creating an asymmetric environment around a transition metal center. Studies directed toward elucidating the mechanism and structures of the catalysts are underway and could offer insight into the mechanism of stereocontrol in these alkylations and aid in designing catalysts for other transformations.

Experimental Section

General Procedure for the Mixed-Ligand Ru(II) Catalyst: [((*R*)-DIFLUORPHOS)(1,2-bis(dimethylphosphino)ethane)Ru-(H)][BPh$_4$] (11). In a nitrogen atmosphere glovebox, a 10-mL Schlenk vessel with a removable Teflon stopcock was charged with $(PPh_3)_3Ru(Cl)(H)$ (81 mg, 0.088, 1 equiv), (*R*)-DIFLUORPHOS (60 mg, 0.088 mmol, 1 equiv), and THF (3.0 mL). The sealed vessel was brought out of the glovebox and then degassed using three freeze−pump−thaw cycles. The reaction mixture was heated to 105 °C for 16 h, then cooled to room temperature and brought back into the glovebox. Then 1,2-bis(dimethylphosphino)ethane (15 μL, 0.088 mmol, 1 equiv) was added and the reaction mixture was stirred for 1 h at rt. Sodium tetraphenylborate (30 mg, 0.088 mmol, 1 equiv) was then added as a 1.0 M solution in THF. The solution was stirred for 12 h at room temperature, then filtered through a pad of Celite. The volatile organic materials were removed in vacuo to afford the crude product. The resulting solid was washed with Et_2O (3 × 1 mL) and benzene (3 × 1 mL) to remove any PPh_3. Further purification was accomplished by precipitation of the Ru(II) complex from a saturated THF solution by slow vapor diffusion with Et_2O at room temperature. The air-sensitive product was sparingly soluble in Et_2O; the catalyst was isolated as an orange solid (85 mg, 77% yield). ^{1}H NMR (THF-d_8, 400 MHz) δ 8.03 (br t, 1H), 7.91 (br t, 1H), 7.72 (br m, 1H), 7.51 (br m, 1H), 7.43−7.33 (m, 16H), 7.30−7.23 (m, 13H), 7.16−6.89 (m, 9H), 6.67 (d, J = 8.4 Hz, 1H), 6.55 (br m, 1H), 1.29−1.25 (m, 6H), 1.14 (br d, J = 7.6 Hz, 3H), 0.88 (m, 1H), 0.65 (br d, J = 7.6 Hz, 1H), 0.51 (br d, J = 8.0 Hz, 1H), 0.27 (br d, J = 8.0 Hz, 3H), 0.04 (d, J = 7.2 Hz, 1H), −18.49 (m, 1H, Ru-*H*). ^{31}P{^{1}H} NMR (THF-d_8, 162 MHz) δ 35.6 (m), 34.1 (m), 30.1 (m), 24.4 (m). HRMS (ESI$^+$) calcd for $[C_{44}H_{41}F_4O_4P_4Ru]^+$: 935.0930. Found: 935.0951.

General Procedure for the Mixed-Ligand-Catalyzed Phosphine Alkylation: (2-(1,3-Dioxolan-2-yl)ethyl)methylphenylphosphine-borane (14b). In a nitrogen atmosphere glovebox, a 1-dram scintillation vial was charged with **11** (7.0 mg, 0.0075 mmol, 0.07 equiv), **4** (10 mg, 0.090 mmol, 1.2 equiv), and THF (0.27 mL). **2** (9.5 μL, 0.075 mmol, 1.0 equiv) and 2-(2-bromoethyl)-1,3-dioxolane (11 μL, 0.090 mmol, 1.2 equiv) were syringed into the solution, and the vial was capped. The reaction solution was stirred at rt for 90 min. The phosphine was then protected as the borane adduct by addition of a 1.0 M solution of BH_3•THF (0.75 mL, 0.75 mmol, 10 equiv). After being stirred for 30 min at rt, the reaction mixture was quenched outside of the glovebox by the slow addition of water; the resulting aqueous solution was extracted with ethyl acetate (4 × 5 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (70:30 hexanes/EtOAc) furnishing the product as a colorless residue (15 mg, 84% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74−7.69 (m, 2H), 7.52−7.45 (m, 3H), 4.88 (t, J = 4.4 Hz, 1H), 3.95−3.81 (m, 4H), 2.03−1.66 (m, 4H), 1.56 (d, J = 10.4 Hz, 3H), 0.61 (br q, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 131.5 (d, J = 9 Hz), 131.4, 129.3 (d, J = 53 Hz), 128.9 (d, J = 10 Hz), 103.5, 103.4, 65.1, 27.3, 21.1 (d, J = 38 Hz), 10.8 (d, J = 39 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 9.8 (q, J_{B-P} = 68 Hz). IR: 3057, 2960, 2885, 2371, 2254, 1436, 1132, 1065, 898, 744, 693, 581 cm^{-1}. HRMS (FAB$^+$) calcd for $[C_{12}H_{19}BO_2P]^+$: 237.1216. Found: 237.1221. Separation of enantiomers by chiral HPLC (Chiralpak AS-H Column, flow rate 1.1 mL/min, 96:4 hexanes/*i*PrOH, T_r minor 21.30, major 23.18 min) determined the ee to be 71%.

General Procedure for the Mixed-Ligand-Catalyzed Phosphine Alkylation of Dihalides: 2,2′-Oxybis(ethane-2,1-diyl)bis-(methylphenylphosphine-borane) (15d). In a N_2atmosphere glovebox, a 1-dram scintillation vial was charged with **11** (7.0 mg, 0.0075 mmol, 0.07 equiv), **4** (10 mg, 0.090 mmol, 1.2 equiv), and THF (0.27 mL). **2** (9.5 μL, 0.075 mmol, 1.0 equiv) and bis(2-bromoethyl)ether (4.8 μL, 0.038 mmol, 0.51 equiv) were syringed into the solution, and the vial was capped. After stirring for 90 min at room temperature, a 1.0 M solution of $BH_3 \cdot$THF (0.75 mL, 0.75 mmol, 10 equiv) was added to the mixture and the resulting solution was stirred for an additional 30 min. The excess borane was quenched outside of the glovebox by the slow addition of water; the resulting aqueous solution was extracted with ethyl acetate (4 × 5 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (75:25 hexanes/EtOAc) furnishing the product as a colorless oil (15 mg, >99% yield). The product was isolated as a mixture of the two diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72−7.68 (m, 4H), 7.53−7.44 (m, 6H), 3.67−.56 (m, 2H), 3.51−3.41 (m, 2H), 2.10−2.02 (m, 4H), 1.57 (d, J = 10.4 Hz, 3H), 1.53 (d, J = 10.4 Hz, 3H), 0.71 (br q, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 131.3, 131.2, 129.5 (dd, J = 54, 16 Hz), 128.7 (dd, J = 10, 2 Hz), 65.4, 27.9 (d, J = 36 Hz), 27.9 (d, J = 36 Hz), 11.5 (d, J = 39 Hz), 11.5 (d, J = 38 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 7.0 (m). IR: 2954, 2920, 2852, 2368, 1436, 1113, 1064, 901, 742, 692 cm^{-1}. HRMS (FAB$^+$) calcd for $[C_{18}H_{29}B_2OP_2]^+$: 345.1880. Found: 345.1885. Separation of enantiomers by chiral HPLC (Chiralpak AS-H Column, flow rate 1.0 mL/min, 97:3 hexanes/EtOH; C_2: T_r major 41.57, minor 45.84 min; meso: T_r 48.44 min) determined the ee to be 94%. The ratio of C_2/meso diastereomers was found to be 68:32.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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