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Enantioselective α-Arylation of Ketones with Aryl Triflates Catalyzed by Difluorphos Complexes of Palladium and Nickel

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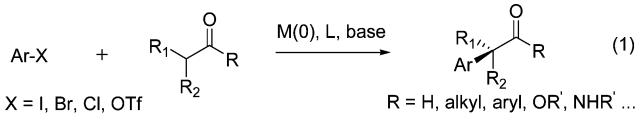
Abstract: The asymmetric α-arylation of ketones with aryl triflates is described, and the use of this electrophile with nickel and palladium catalysts containing a segphos derivative increases substantially the scope of highly enantioselective arylations of ketone enolates. The combination of aryl triflates as reactant, difluorphos as ligand, palladium catalysts for reactions of electron-neutral or electron-rich aryl triflates, and nickel catalysts for reactions of electron-poor aryl triflates led to a series of α-arylations of tetralone, indanone, cyclopentanone, and cyclohexanone derivatives. Enantioselectivities ranged from 70% to 98% with 10 examples over 90%. Systematic studies on these α-arylations have revealed a number of factors that affect enantioselectivity. Ligands containing biaryl backbones with smaller dihedral angles generate catalysts that react with higher enantioselectivity than related ligands with larger dihedral angles. In addition, faster rates for reactions of aryl triflates versus those for reactions of aryl bromides allow the α-arylations of aryl triflates to be conducted at lower temperatures, and this lower temperature improves enantioselectivity. Finally, studies that compare the enantioselectivities of catalytic reactions to those of stoichiometric reactions of isolated [(segphos)Pd(Ar)(Br)], [(segphos)Pd(Ar)(I)], and [(segphos)Ni(C_6H_4-4-CN)Br] suggest that catalyst decomposition affects enantioselectivity.

Introduction

Methods to generate quaternary stereocenters enantioselectively remain under development.[1−3] Catalytic asymmetric α-arylation is an attractive method to construct such stereocenters because of the common occurrence of benzylic quaternary stereocenters in biologically active natural and unnatural products. Catalytic asymmetric α-arylation of carbonyl compounds (eq 1) can not only generate benzylic stereocenters α to a carbonyl group, but it can generate benzylic stereocenters in chiral, nonracemic materials containing other functionality because of the versatility of the carbonyl group. For example, this asymmetric α-arylation could ultimately be used to generate a benzylic stereocenter α to a hydroxyl group after reduction or α to an amino group after reductive amination.



(1)

Although enantioselective reactions of aryl and vinyl halides with ketones,[4−6] amides,[7,8] lactones,[9] and β-ketoesters[10] catalyzed by palladium, nickel, and copper catalysts have been reported, the scope of these reactions remains narrow. For example, the α-arylation of 2-methyltetralone catalyzed by palladium−BINAP complexes occurs in 61−88% ee with meta- and para-substituted bromoarenes, and the reactions of 2-methyl indanone occurred in only 70% ee with meta-substituted bromoarenes and formed racemic product with para-substituted bromoarenes.[4] A similar issue in reaction scope was observed for the reactions of cyclohexanone and cyclopentanone derivatives. The reaction of a 2-methylcyclopentanone derivative with a number of aryl bromides occurred with high enantioselectivity,[5] but the reactions of a 2-methylcyclohexanone derivative occurred with low enantioselectivity.[4] Likewise, the α-vinylation of five-membered cyclic ketones occurred in high ee with electron-rich, sterically hindered versions of Hayashi's MOP ligand, but few reactions of six-membered cyclic ketones were reported, and these occurred with low enantioselectivity.[6]

In addition to these limitations on reaction scope, little information has been gained on the factors that control stereoselectivity. To date, the development of these reactions has been largely empirical. For example, studies on the step that controls enantioselectivity, the origin of the role of halide in controlling enantioselectivity, and the effect of catalyst stability

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(2) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389.
(3) Douglas, C. J.; Overmann, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *42*, 1688.
(4) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.
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(8) Arao, T.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1743.
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or instability on enantioselectivity have not been reported. Moreover, the structural features of bisphosphines containing biaryl backbones that control enantioselectivity have not been revealed.

Finally, the α-arylation of ketones has focused on reactions of aryl halides, and asymmetric α-arylation of carbonyl compounds using aryl triflates has not been reported. These reagents are important to develop as electrophiles for this enantioselective chemistry because of their accessibility from phenols and because the identity or precise structures of intermediates involved in transmetalation with arylpalladium triflate complexes could be different from those involved in transmetalation with organopalladium halide complexes. Moreover, the higher reactivity of aryl triflates could allow the α-arylations with these electrophiles to be conducted at lower temperatures than the reactions with aryl halides, and one could envision obtaining higher enantioselectivities at these lower reaction temperatures.

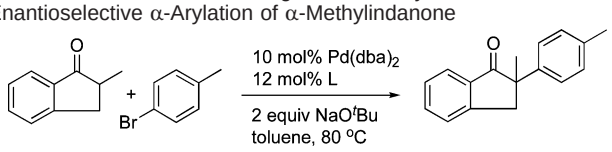
Herein, we describe the first α-arylations of ketones using aryl triflates. Systematic studies on these α-arylations have revealed a number of factors that contribute to the control of enantioselectivity. These studies begin to show the structural and electronic features of biarylphosphines that control ee, the effect of the leaving group on enantioselectivity, and the origin of this effect of leaving group. In addition, studies that compare the enantioselectivity of catalytic reactions and of stoichiometric reactions of isolated arylpalladium complexes have revealed an effect of catalyst decomposition on the stereoselectivity. Ultimately, a combination of palladium and nickel catalysts ligated by difluorphos for reactions of two classes of aryl triflate electrophiles gives rise to a broad range of α-arylations of ketones that occur with high enantioselectivity.

Results and Discussion

Because the α-arylations of ketones catalyzed by complexes of BINAP occured with modest enantioselectivity in many cases, we investigated ligands that could improve the scope of highly enantioselective α-arylations of ketones. These studies revealed several factors that ultimately led to the final systems that catalyze the enantioselective α-arylation of five- and six-membered cyclic ketones with both electron-rich and electron-poor aryl triflates. These factors include a small dihedral angle in the backbone of the chiral bisphosphine, the use of a somewhat electron-poor bisphosphine ligand, the use of a bisphosphine ligand that resists P−C bond cleavage, the use of aryl triflates as electrophiles, and the use of one metal for reactions of electron-neutral and electron-rich aryl triflates and a second metal for reactions of electron-poor aryl triflates. These effects and the resulting scope of the α-arylations are described in the following sections.

1. Effect of Ligand Dihedral Angle and Electronic Properties. One structural feature of biaryl-linked bisphosphines that has been thought to affect enantioselectivity of many types of metal-catalyzed reactions is the backbone dihedral angle.[11]

Table 1. Effect of Dihedral Angle of the Biaryl Backbone on Enantioselective α-Arylation of α-Methylindanone



entry	ligand	dihedral angle (deg)	ee (%)[a]
1	(*R*)-tol-binap		6
2	(*R*)-binap	87	9
3	(*R*)-MeO-biphep	87	11
4	(*R*)-segphos	67	72
5	(*R*)-difluorphos	67	78

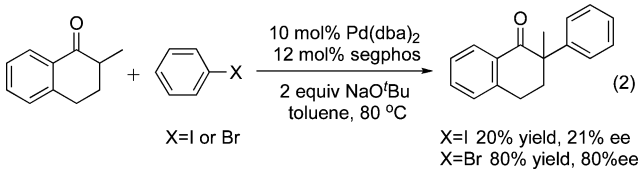
[a] Determined by chiral HPLC.

To determine if this parameter significantly influences the rate and selectivity of the α-arylation of ketones, we studied reactions catalyzed by palladium complexes possessing varied dihedral angles in the ligand backbone.

The results of a study of the effect of dihedral angle on the α-arylation of α-methyl indanone are summarized in Table 1. The dihedral angles used in this analysis are literature values derived from MM2 calculations of the free ligand.[12,13] The data in Table 1 illustrate a dramatic effect of the dihedral angle of the biaryl-linked bisphosphines on enantioselectivity. The magnitudes of the ee values increased with decreasing dihedral angles. These data led us to focus our subsequent studies on the segphos family of ligands.

The data in Table 1 also illustrate that the electronic properties of the biarylphosphine influenced enantioselectivity. This electronic effect was revealed by a comparison of the selectivity of the reactions conducted with segphos and the more recently reported difluorphos, which contains two difluoromethylene units in the backbone of the ligand. The reaction of the α-methyl indanone occurred with higher enantioselectivity when catalyzed by the complex containing difluorphos as ligand than when catalyzed by the complex containing segphos as ligand.

2. Effect of Leaving Group on Rate and Enantioselectivity. Several pieces of data imply that the leaving group on the aryl electrophile also affects enantioselectivity. These data are summarized in eq 2. First, the reaction of α-methyltetralone



(2)

with *p*-iodotoluene formed the coupled product in only 21% ee, whereas the same reaction with *p*-bromotoluene formed the coupled product in 80% ee. The reaction of iodotoluene also occurred in a low 20% yield.

This observation that the identity of the halide affected the enantioselectivity led us to investigate the reactions of aryl

(11) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

(12) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223.

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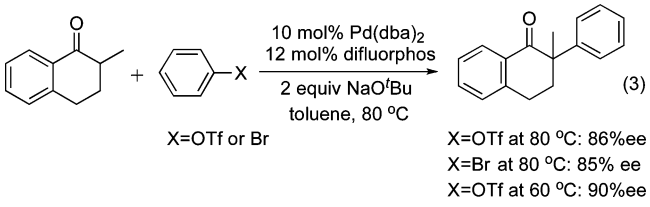
triflates. As shown in eq 3, this reaction occurred with high enantioselectivity. At 80 °C the enantioselectivity of the α-arylation with phenyl triflate was similar to that of the reaction of the phenyl bromide. However, the reaction of phenyl triflate occurred faster than the reaction of phenyl bromide. Thus, this reaction could be conducted at a lower temperature, and this lower temperature led to an asymmetric α-arylation of α-methyl tetralone that occurred with bromobenzene in a higher 90% ee.



(3)

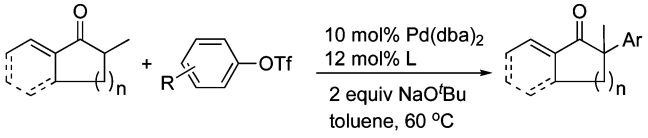
3. Scope of the Palladium-Catalyzed α-Arylations with Aryl Triflates. The scope of the α-arylation of cyclic ketones with aryl triflates catalyzed by the combination of $Pd(dba)_2$ and difluorphos is summarized in Table 2. These examples include reactions of α-methyl tetralone, α-methyl indanone, 2-methyl 6-benzylidene cyclohexanone, and 2-methyl 5-benzylidene cyclopentanone with a variety of aryl triflates that are electron-neutral and electron-rich.

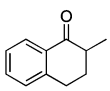
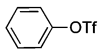
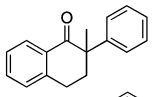
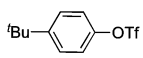
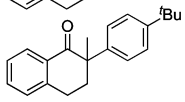
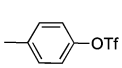
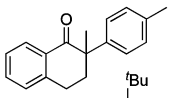
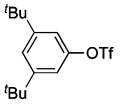
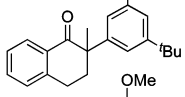
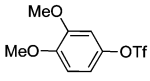
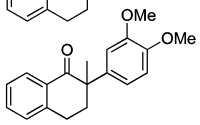
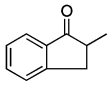
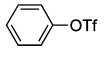
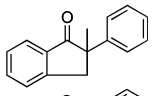
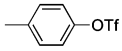
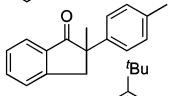
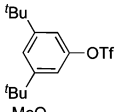
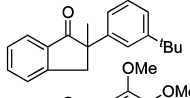
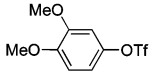
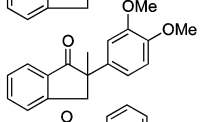
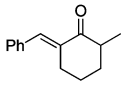
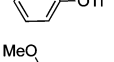
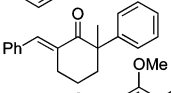
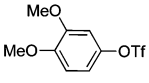
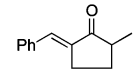
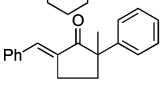
The reactions catalyzed by the difluorphos palladium species occurred in high ee and high yield in many cases with aryl groups containing meta or para substituents. The reactions of α-methyl tetralone occurred in over 90% ee with aryl triflates containing both meta and para substituents. The reactions of α-methylindanone with aryl triflates were faster than those of α-methyltetralone and occurred with substantial enantioselectivities. For example, reactions of meta-substituted aryl triflates (Table 2 entries 8 and 9) occurred with 2-methylindanone in >80% ee.

The enantioselectivities obtained with difluorphos as ligand were typically higher than those obtained with BINAP as ligand. For example, the reaction of *p*-tolyl triflate with α-methylindanone catalyzed by the difluorphos-ligated catalyst (Table 2, entry 7) gave product in 78% ee, whereas the same reaction catalyzed by the complex containing BINAP formed nearly racemic product. Likewise, the reaction of 2-methyltetralone with bromobenzene catalyzed by BINAP and Pd(0) led to the coupled product in only 73% ee, but the reaction of these substrates catalyzed by difluorphos and Pd led to the coupled product in 90% ee (Table 2, entry 1). The reactions of the cyclohexanone derivative with two different aryl triflates (Table 2, entries 10 and 11) formed the product in a modest 78% and 77% ee, but these values are presumably higher than the "very low ee's" obtained in previous work with BINAP as ligand.[4] The reaction of 2-methyl 6-benzylidene cyclopentanone with phenyl triflate (Table 2, entry 12) occurred in 95% ee; this result is still slightly higher than the value (92% ee) obtained in previous work with BINAP as ligand.[4]

To determine the absolute configuration of one of the α-arylation products, we synthesized an iodide derivative of

Table 2. Asymmetric α-Arylation of Ketones with Aryl Triflates Catalyzed by $Pd(dba)_2$/Difluorphos[a]

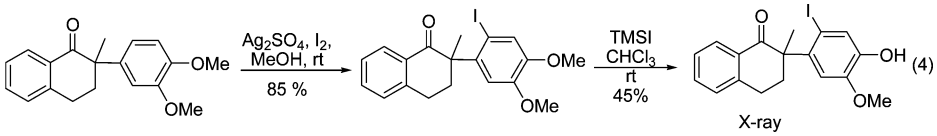


Entry	ketone	ArOTf	product	isolated yield
1				81%, 90%ee
2				85%, 92%ee
3				79%, 92%ee
4				83%, 95%ee
5				79%, 91%ee
6				77%, 70%ee
7				79%, 78%ee
8				84%, 89%ee
9				78%, 82%ee
10				80%, 78%ee
11				70%, 77%ee
12				70%, 95%ee

[a] L: difluorphos; ee determined by chiral HPLC.

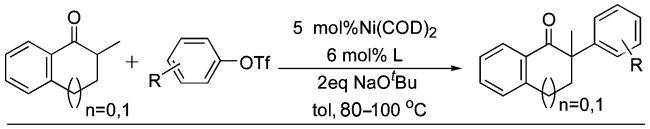
2-methyl-2-(3,4-di-methoxyphenyl)-tetralone (eq 4) and obtained X-ray structural data. To obtain crystalline samples, the product was iodinated, and this iodination product was subjected to demethylation conditions to produce an iodo, hydroxyphenyl derivative. The results of an X-ray structural study show that the α-arylation product formed from the reaction conducted with the R enantiomer of difluorphos possesses an R configuration.

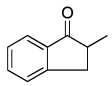
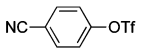
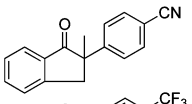
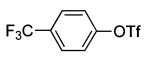
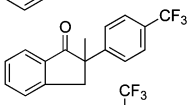
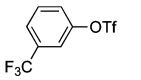
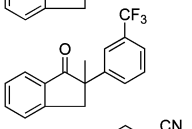
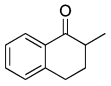
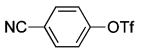
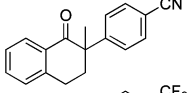
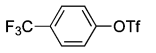
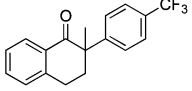
4. Nickel-Catalyzed Asymmetric α-Arylation of Ketones. The reactions of ketones with electron-poor aryl triflates



(4)

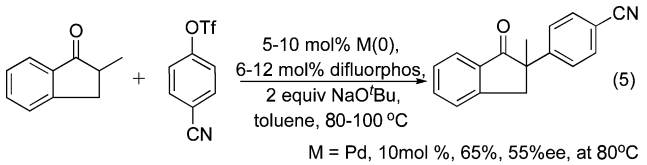
Table 3. Asymmetric α-Arylation of Ketones with Aryl Triflates Catalyzed by $Ni(COD)_2$/Difluorphos (L: Difluorphos)



Entry	ketone	ArOTf	product	isolated yield
1				84%[a], 95%ee
2				69%[a], 96%ee
3				70%[a], 86%ee
4				55%[b], 97%ee
5				40%[b],98%ee

[a] At 80 °C. [b] At 100 °C.

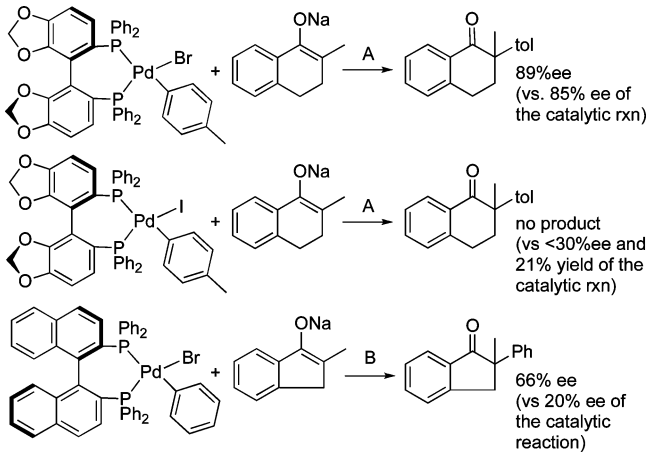
catalyzed by the palladium catalyst occurred with much lower enantioselectivities than did reactions of electron-neutral or electron-rich aryl triflates. For example, the reaction of α-methyl indanone with 4-cyanophenyl trifluoromethanesulfonate shown in eq 5 formed the coupled product in a moderate ee of 55%.



This limitation was overcome by using a nickel catalyst containing the same difluorphos ligand. The same reaction of α-methyl indanone with 4-cyanophenyl triflate catalyzed by the combination of $Ni(COD)_2$ and difluorphos as ligand formed the coupled product in 95% ee (eq 5). This reaction constitutes the first enantioselective α-arylation with 2-methyl-1-indanone to occur in 95% ee or higher.[14]

Table 3 shows the scope of the enantioselective α-arylation of ketones with electron-poor aryl triflates catalyzed by 5 mol % $Ni(COD)_2$ and 6 mol % difluorphos. In addition to the high enantioselectivity for the reaction of 2-methylindanone with 4-cyanophenyl triflate shown in entry 1, the reactions of α-methyl indanone with 3- and 4-trifluoromethylphenyl triflate

Scheme 1 [a]



[a] Conditions: (A) 1:1 ratio of Pd(II) complex to sodium enolate, toluene, 1 equiv of segphos, 80 °C, 1 h; (B) 1:1 ratio of Pd(II) complex to sodium enolate, toluene, 1 equiv of BINAP, 80 °C, 1 h.

formed the coupled product in 86% and 96% ee, respectively. The reactions of α-methyl tetralone with electron-poor aryl triflates were similarly selective. Although these reactions formed the coupled product in lower yield, the reactions of 4-cyanophenyl and 4-trifluoromethylphenyl triflate occurred in 97% and 98% ee. Because the electron-poor aryl triflate underwent hydrolysis under the strongly basic conditions at the temperatures and times required for high conversion, an excess of aryl triflate was employed in this set of reactions.

5. Comparisons of Selectivities from Stoichiometric and Catalytic Reactions.

5.1. Enantioselectivity of Reactions of Enolates with Arylpalladium Halide Complexes. To identify the palladium species that controls the enantioselectivity, we conducted stoichiometric reactions of Pd(segphos)(tol)(Br) and Pd(segphos)(tol)(I) with sodium enolates, and compared the yields and enantioselectivities from these stoichiometric reactions to each other and to those of the corresponding catalytic reactions. These reactions were conducted with the segphos complexes because the ee's are close to those obtained with difluorphos, and substantial amounts of this ligand were made available (see the Acknowledgements). Reactions were conducted with the arylpalladium halide complexes because the arylpalladium triflate species are typically too unstable to isolate, and the selectivities of the bromide and triflate complexes were similar at the same reaction temperatures.

The arylpalladium halide complexes ligated by segphos and BINAP were prepared by two different procedures.[15,16] The arylpalladium bromide complexes were prepared by the reaction of segphos with $\{Pd[P(o\text{-tol})_3](Br)(p\text{-tol})\}_2$,[15] whereas the arylpalladium iodide complexes were prepared by the reaction of segphos with [PdI(*p*-tol)(TMEDA)].[16] These segphos compounds were characterized by standard NMR spectroscopic methods and elemental analysis.

The origin of the effect of leaving group on ee was revealed by comparing the stoichiometric reactions of the sodium enolate of α-methyl tetralone with the arylpalladium bromide and iodide

(14) Recently, Chen et al. reported reactions of aryl bromides with 2-methyl indanone and 2-methyl tetralone catalyzed by the combination of $Ni(COD)_2$ and P-PHOS in high ee's. To compare the selectivities in Table 3 to those with the catalyst containing P-PHOS, we conducted the reactions of 2-methyltetralone with 4-bromobenzonitrile under the reported conditions. We have been unable to obtain the same high ee's as were reported. In the hands of several different investigators in our laboratory with different batches of $Ni(COD)_2$ and two different suppliers of NaO^tBu we obtained 38−46% ee for the reaction of 2-methyltetralone with 4-bromobenzonitrile. Thus, the reactions in Table 3 comprise a set of α-arylations that occur with higher enantioselectivities than we have been able to obtain with any other catalyst. See: Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413.

(15) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, L. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618.

(16) Markies, B. A.; Canty, A. J.; de Graaf, W.; Boersma, J.; Janssen, M. D.; Hogerheide, M. P.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1994**, *482*, 191.

complexes. These data are summarized in Scheme 1. Reaction of the isolated *p*-tolylpalladium bromide complex with this enolate in the presence of 1 equiv of segphos to trap the Pd(0) species formed the α-aryl ketone in 75% yield and 89% ee after 1 h at 80 °C. The conditions for reaction of this complex with the enolate and the comparable yield of this reaction to that of the catalytic process show that this species is kinetically competent to be an intermediate in the reaction. Most important, the 89% ee of this stoichiometric reaction is similar to the 85% ee observed from the catalytic process.

In contrast, the reaction of the *p*-tolylpalladium iodide complex with the same enolate formed none of the α-aryl ketone product. Instead, ketone, biphenyl, PPh_3, and PPh_2(*p*-tol) were observed by GC−MS. This result leads to several conclusions. First, the low yield of the catalytic process conducted with iodoarenes results from the low yield of the transmetalation and reductive elimination sequence involving Pd(segphos)(tol)(I). Second, the product generated from the catalytic process does not form from the arylpalladium iodide intermediate ligated by segphos. Instead, the small amount of α-aryl ketone more likely forms through a different intermediate, and the factors that control the enantioselectivity of the α-arylations with iodoarenes are unlikely to be related to those that control the enantioselective reactions of segphos or binap-ligated arylpalladium halide or triflate complexes with enolates. Perhaps a product from decomposition of the arylpalladium iodide complex catalyzes the formation of the small amount of coupled product observed from reactions of iodoarenes.

A comparison of the catalytic and stoichiometric reactions of BINAP-ligated arylpalladium bromide complexes revealed potential influences of catalyst decomposition on enantioselectivites. The reaction of the sodium enolate of α-methyl indanone with the phenylpalladium bromide complex of BINAP formed the coupled product in 66% ee. This value is much higher than the 20% ee obtained from the catalytic reaction in the presence of the palladium complex of BINAP. This result implies that a large portion of the product of the reactions of 2-methylindanone with bromoarenes catalyzed by BINAP-ligated palladium is formed from an intermediate other than (BINAP)Pd(Ar)(Br).

Additional experiments revealed one more side reaction that further complicated the α-arylation of ketones and that could be leading to catalyst decomposition. Attempts to prepare (BINAP)Pd(tol)(Br) led to the formation of products from exchange of the phosphorus-bound and palladium-bound aryl groups by P−C bond cleavage, whereas (segphos)Pd(tol)(Br) was stable to exchange of these aryl groups under the same conditions. Thus, P/C bond cleavage of the BINAP complexes is faster than P−C bond cleavage of the segphos complex, and this mode of reactivity could ultimately lead to cleavage of the phosphorus from the biaryl backbone to form a less selective complex of a monophosphine.[15,17]

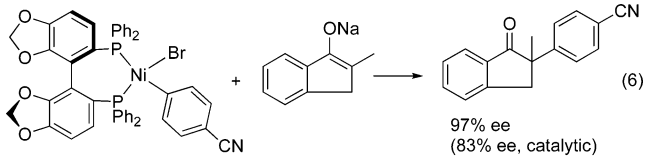
One might speculate that the difference in enantioselectivity from reactions of palladium complexes containing BINAP and segphos or difluorphos might be due solely to catalyst stability. However, we emphasize that the enantioselectivities from the stoichiometric reactions of (segphos)Pd(Ar)(Br) with the sodium enolate of 2-methylindanone is higher than that of (BINAP)-Pd(Ar)(Br) with the same enolate.

(17) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441.

5.2. Enantioselectivity of Reactions of Enolates with Arylnickel Halide Complexes. Nickel-catalyzed couplings are often considered to occur by Ni(I) intermediates,[18−20] rather than through arylnickel(II) halide intermediates. Thus, we sought to determine if the Ni(II) complexes (segphos)Ni(Ar)(X) were kinetically and chemically competent to be intermediates in the nickel-catalyzed asymmetric α-arylation. To do so, we prepared (segphos)Ni(C_6H_4-4-CN)(Br) and studied its reactions with sodium enolates.

The arylnickel halide complex (segphos)Ni(C_6H_4-4-CN)(Br) was isolated in 50% yield from the reaction of $(PPh_3)_2$Ni(C_6H_4-4-CN)(Br) with segphos. The product was characterized by conventional NMR spectroscopy and elemental analysis.

The stoichiometric reaction of the sodium enolate of 2-methylindanone with (segphos)Ni(C_6H_4-4-CN)Br yielded the α-aryl ketone in 90% yield after 3 h at 80 °C. Thus, (segphos)Ni-(C_6H_4-4-CN)Br is kinetically competent to be an intermediate in the nickel-catalyzed α-arylation. In addition, the product of this reaction was formed in 97% ee. This enantioselectivity is higher than the 83% ee of the catalytic reaction of 4-bromobenzonitrile with 2-methylindanone. Thus, the reaction of (segphos)-Ni(C_6H_4-4-CN)Br with the sodium enolate of 2-methylindanone is sufficiently stereoselective to be involved in the C−C bond formation. The slightly lower ee of the catalytic process suggests that some of the product is formed from a less selective catalyst. If this second catalyst lacked a chiral ligand, approximately 7% of the product would be formed from such a species. In order to test the hypothesis that a product from decomposition of the segphos−nickel species catalyzes the formation of product with lower enantioselectivity we conducted the catalytic reaction with 20 mol %, instead of 5 mol %, $Ni(COD)_2$. If enantioselectivity is affected by catalyst stability, then reactions with this higher loading should occur with higher enantioselectivity. Indeed, the reaction with 20 mol % catalyst occurred in a higher 92% ee.



Conditions: 1:1 ratio of Ni(II) complex and sodium enolate, toluene, 1 equiv segphos, 3 h, 80 °C.

6. Summary and Conclusions. In summary, we have described the first examples of the catalytic enantioselective α-arylation of ketone enolates with aryl triflates. These reactions were conducted with a bisphosphine containing a biaryl backbone that has a small dihedral angle. The combination of aryl triflates as reactant, difluorphos as ligand, a palladium catalyst for reactions of electron-neutral and electron-rich aryl triflates, and a nickel catalyst for reactions of electron-poor aryl triflates led to a series of α-arylations that occur in much higher enantioselectivity than the previously reported reactions of aryl bromides with other catalysts.

In addition to this improvement in the scope of highly enantioselective C−C bond-forming reactions, these studies revealed a series of factors that control enantioselectivity. First,

(18) Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262.
(19) Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1986**, *108*, 719.
(20) Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100.

the smaller dihedral angle of segphos and difluorphos appears to create complexes that react with higher enantioselectivity than complexes of related ligands with larger dihedral angles. This effect has been attributed in previous studies to enhanced steric effects. It has been proposed that the smaller dihedral angle causes the aryl groups of the phosphine to project closer to the incoming substrates.[11] Second, the faster reactions of aryl triflates versus aryl bromides allows the reactions to be conducted at lower temperature, and this lower temperature leads to higher enantioselectivity. Third, the identity of the halide or pseudohalide can affect enantioselectivity by altering the ability of the complex to undergo transmetalation and by affecting the stability of the catalyst. Fourth, an appropriate pairing of the catalyst with the electronic properties of the aryl group, although empirical, leads to a set of α-arylation processes that encompass reactions of electron-rich, electron-neutral, and electron-poor aryl triflates. Fifth, the stability of the ligand toward P−C bond cleavage affects reaction yield and might affect the stability of the catalyst toward formation of achiral or less selective chiral catalysts. Ultimately, the identification and control of a combination factors that dictate enantioselectivity has led to reactions that are selective enough for applications in complex molecule synthesis. Studies on the applications of this reaction are ongoing.

Experimental Section

General Methods. Reactions were conducted using standard drybox techniques. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 400 or 500 MHz spectrometer with tetramethylsilane or residual protiated solvent used as a reference, and coupling constants are reported in hertz (Hz). Chromatographic purifications were performed by flash chromatography using silica gel (200−400 mesh) or preparative TLC. The yields of the coupled products included in all tables refer to isolated yields. Products that had been reported previously were isolated in greater than 95% purity, as determined by ^{1}H and ^{13}C NMR, and copies of spectra are provided in the Supporting Information. All ^{13}C NMR spectra were proton decoupled. Enantioselectivities were measured by HPLC using the indicated columns and conditions.

Representative Procedure for the Asymmetric Arylation of Ketones with Aryl Triflates Using Pd(0)/Difluorphos (Table 2, Entry 1). To a screw-capped vial containing difluorphos (8.2 mg, 0.012mmol), $Pd(dba)_2$ (5.8 mg, 0.010mmol), NaO^{t}Bu (19.2 mg, 0.200 mmol), and 2-methyltetralone (16.0 mg, 0.100 mmol) in toluene (2.0 mL) was added phenyl triflate (31.4 mg, 0.200 mmol). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred at 60 °C for 48 h. The crude reaction mixture was then cooled to room temperature, and the reaction was quenched with ice water. The resulting solution was then diluted with ethyl acetate (15 mL) and washed with brine. The organic phase with dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The residue was then purified by preparative TLC (hexane/ether = 97:3) to provide 19.1 mg (81% yield) of product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.45 (s, 3H), 2.12−2.22 (m, 1H), 2.51−2.57 (m, 1H), 2.71−2.77 (m, 2H), 7.03 (d, J = 7.6 Hz, 1H), 7.09−7.26 (m, 6H), 7.33 (td, J = 7.3, 1.4 Hz, 1H), 8.08 (dd, J = 7.8, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.3, 27.3, 36.5, 50.7, 126.6, 126.8, 126.9, 128.2, 128.8, 128.9, 132.9, 133.3, 142.3, 143.8, 201.6. Chiral HPLC conditions: Chiralcel AD-H column; solvent, hexane/isopropyl alcohol (96.5/3.5); flow rate, 0.5 mL/min; UV lamp, 254 nm. $[\alpha]^{26}_D$ = +179 (c = 0.24, $CHCl_3$).

Representative Procedure for the Asymmetric Arylation of Ketones with Aryl Triflates Using Ni(0)/Difluorphos (Table 3, Entry 1). To a screw-capped vial containing difluorphos (10.3 mg, 0.0150 mmol), $Ni(COD)_2$ (3.5 mg, 0.016mmol), NaO^{t}Bu (48.0 mg, 0.500mmol), and 2-methylindanone (36.5 mg, 0.250 mmol) in toluene (2.0 mL) was added 4-cyanophenyl trifluoromethanesulfonate (188 mg, 0.750 mmol). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred at 80 °C for 60 h. The crude reaction mixture was then cooled to room temperature, and the reaction was quenched with ice water. The resulting solution was then diluted with ethyl acetate (20 mL) and washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The residue was then purified by chromatography on silica gel, eluting with hexane/ether (80:20) to provide the 54.6 mg (84% yield) of the product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.59 (3H, s), 3.27 (1H, d, J = 17.4 Hz), 3.48 (1H, d, J = 17.4 Hz), 7.35−7.39 (3H, m), 7.43 (1H, d, J = 7.9 Hz), 7.51 (2H, d, J = 8.4 Hz), 7.60 (1H, t, J = 7.4 Hz), 7.74 (1H, d, J = 7.8 Hz). ^{13}CNMR ($CDCl_3$, 125 MHz): δ 23.5, 43.3, 52.2, 109.5, 117.7, 124.1, 125.5, 126.1, 127.1, 131.3, 134.0, 134.6, 148.2, 151.0, 206.3. Anal. Calcd. For $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.27; H, 5.28; N, 5.65. Chiral HPLC conditions: Chiralcel OB-H column; solvent, hexane/isopropyl alcohol (80/20); flow rate, 1.0 mL/min; UV lamp, 254 nm. $[\alpha]^{26}_D$ = −56.7 (c = 0.22, $CHCl_3$).

Acknowledgment. We thank the NIH (NIGMS GM-58108) for support of this work. We also thank Takasago Int. Co. for gifts of segphos and Johnson-Matthey for a gift of palladium salts.

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

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