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Palladium-Catalyzed Enantioselective α-Arylation of α-Fluoroketones

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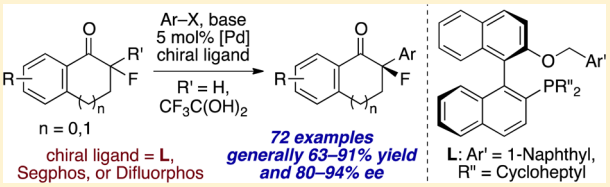
Supporting Information

ABSTRACT: The transition-metal-catalyzed α-arylation of carbonyl compounds is a widely practiced method for C−C bond formation. Several enantioselective versions of this process have been reported, but intermolecular, enantioselective coupling reactions of aryl electrophiles with α-fluoro carbonyl compounds have yet to be disclosed. We report enantioselective coupling of aryl and heteroaryl bromides and triflates with α-fluoroindanones catalyzed by palladium complexes of a BINOL-derived monophosphine and Segphos, respectively. The enolates were generated directly from α-fluoroindanones in the presence of potassium phosphate base during the reactions. We also report that reactions of α-fluorotetralones occur in high yields and enantioselectivities when conducted with enolates generated by elimination of trifluoroacetate from trifluoromethyl β-diketone hydrates. These reactions were catalyzed by palladium complexes of the commercially available bisphosphine Difluorphos. Thus, the formation of enantioenriched α-aryl-α-fluoroketones can be readily achieved by C−C bond formation when the appropriate palladium catalyst and α-fluoro enolate precursor were used.



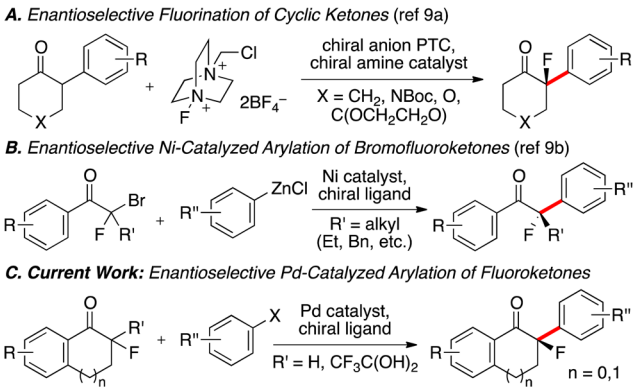
INTRODUCTION

α-Aryl carbonyl compounds are widespread in medicinal chemistry and are often employed in natural product synthesis as both intermediates and target molecules.[1] Among this class of compounds, α-aryl-α-fluoro carbonyl compounds are particularly interesting structures because they can be mimics of α-hydroxy carbonyl compounds[2] or serve as non-enolizable analogues of α-aryl carbonyl compounds containing tertiary α-stereocenters.[3] One commercially important α-aryl-α-fluoro carbonyl compound is the potassium channel opener MaxiPost (BMS-204352).[4] In addition to their value as final structures, α-fluoro carbonyl compounds are versatile synthetic intermediates that can be converted to a wide array of chiral nonracemic mono-fluorinated alcohols, ethers, esters, amines, and amine derivatives.

Although α-aryl α-fluoro carbonyl compounds are valuable and the α-carbon atom is a stereogenic center in most examples, enantioselective methods to form these classes of molecules are limited.[2b,5] Most methods to form enantioenriched α-fluoro carbonyl compounds are suitable to form secondary[6] but not tertiary α-fluoro stereogenic centers,[7] or they require β-dicarbonyl compounds.[8] Enantioenriched secondary α-fluoro carbonyl compounds can be valuable, but they bear an enolizable α-C−H bond and, therefore, are less configurationally stable than their tertiary α-fluoro carbonyl counterparts, which lack an enolizable C−H bond.

Methods for the enantioselective formation of tertiary α-fluoro carbonyl compounds by the α-functionalization of enolates can be divided into two reaction classes: (1) electrophilic fluorination reactions of α-disubstituted enolates,[7a−e,8a] and (2) nucleophilic addition reactions of α-fluoro enolates,[7f−i,8b−d] which often proceed by aldol, Mannich and Michael-type pathways. However, methods for the syntheses of enantioenriched, α-aryl-α-fluoroketones with fully substituted α-stereocenters are particularly scarce.[9] Toste and co-workers reported enantioselective fluorinations of cyclic ketones via cooperative catalysis of an enamine and a chiral, anionic phase-transfer catalyst, but this method requires SelectFluor to be the limiting reagent (Scheme 1A).[9a] Fu and Liang disclosed nickel-catalyzed reactions of racemic α-bromo-

Scheme 1. Enantioselective Methods for the Syntheses of α-Aryl-α-fluoroketones



Received: September 12, 2016
Published: November 4, 2016

DOI: 10.1021/jacs.6b09580
J. Am. Chem. Soc. 2016, 138, 15980−15986

α-fluoroketones and arylzinc reagents, but this method requires pre-functionalization of the ketone reactants and conversion of aryl halides to their organozinc derivatives (Scheme 1B).[9b] No direct, intermolecular enantioselective coupling of aryl halides or pseudohalides with fluorinated carbonyl compounds has been reported.

The coupling of α-fluoroketones with aryl electrophiles is challenging to achieve for many reasons. First, little is known about the types of catalysts and reaction conditions that are needed for the reactions to occur. Therefore, it is unclear whether one should focus on reactions catalyzed by monophosphines or bisphosphines. One set of direct cross-couplings of α-fluoroketones with aryl bromides has been published, and this process was conducted with achiral catalysts containing monophosphine ligands, such as P(*t*-Bu)$_3$, P(*o*-Tol)$_3$, and the dialkylbiarylphosphine RuPhos.[10] The single enantioselective α-arylation of an α-fluoro enolate occurs to form a lactam and is intramolecular. This reaction occurred with a C_2-symmetric monodentate *N*-heterocyclic carbene ligand.[7h]

Second, the properties of α-fluoro enolates are significantly different from their nonfluorinated analogues. α-Fluoro enolates are less nucleophilic than nonfluorinated enolates,[11] and α-fluoro enolates are more challenging to generate than their nonfluorinated counterparts because they are typically unstable to soluble strong bases. Thus, conditions appropriate for generating α-fluoro enolates are more limited than those for generating nonfluorinated enolates. Furthermore, the parent α-fluoroketones are susceptible to protodefluorination under various reaction conditions.[10d,12] Thus, the relative rates of generation and consumption of the fluoro enolates by transmetalation must be matched to avoid accumulation of an alkali metal enolate that undergoes protodefluorination. Prior work on the direct coupling of fluorinated ketone enolates generated low concentrations of the enolate with weak phosphate bases. Reactions conducted with stronger bases, such as KO*t*-Bu or KHMDS, did not form product or were very limited in substrate scope.[10b,d]

Finally, the rate of reductive elimination of fluoroalkylpalladium complexes is generally slower than that of their nonfluorinated analogues.[13] This slow rate of reductive elimination could cause the catalytic reaction to require temperatures at which the enolates of α-fluoroketones are unstable or the reaction is no longer highly enantioselective. In addition, the C−C coupling of α-fluoro enolates may be slower than other processes mediated by palladium catalysts, such as biaryl coupling, or β-hydride elimination from Pd-enolate complexes and subsequent aryl−H reductive elimination.

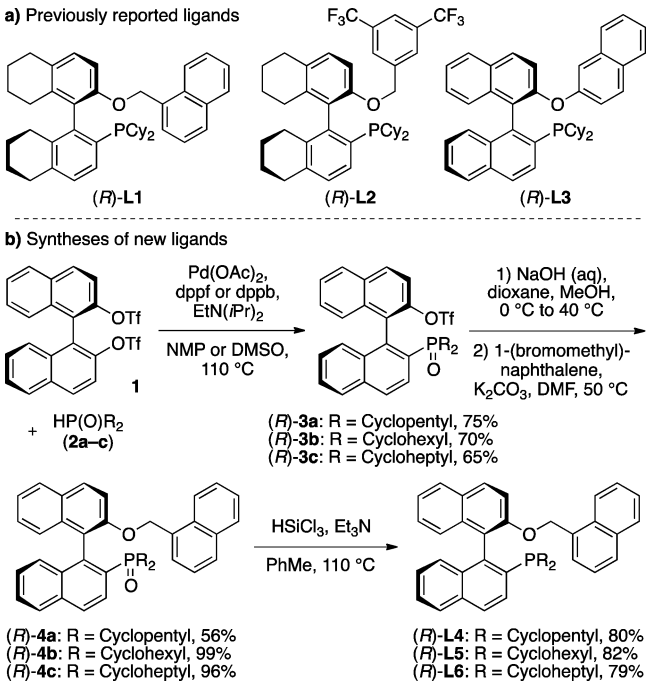
We report the Pd-catalyzed enantioselective α-arylation of α-fluoroindanones and tetralones with aryl and heteroaryl bromides and triflates. We show that the coupling of these enolates occurs in high yield and enantiomeric excess (ee) with distinct sets of catalysts and conditions. The coupling of α-fluorotetralones occurs in high yields and ee's with commercially available Difluorphos ligand and enolates generated by elimination of trifluoroacetate from trifluoromethyl β-diketones. In contrast, the reactions of α-fluoroindanones occur in high yields and ee's when conducted with an enolate generated directly from the carbonyl compound and with a catalyst containing a new BINOL-derived chiral monophosphine containing dicycloheptylphosphino and 1-naphthylmethyl ether substituents. Once these conditions stemming from the different properties of these fluorinated enolates are established, a wide range of aryl and heteroaryl bromides and triflates couple in high yields and ee's with both indanones and tetralones possessing varied electronic properties. In this manner a route to these products is established by C−C bond formation with widely available (pseudo)haloarenes and heteroarenes, rather than enantioselective C−F bond formation.

RESULTS AND DISCUSSION

Our studies to develop enantioselective α-arylation of α-fluoroketones focused on reactions of α-fluoroindanones and α-fluorotetralones. The cyclic structures of these ketones ensure the formation of enolates having one predefined (*Z*) geometry, but the differences in ring size, bond angles, and thermodynamic acidity between indanones and tetralones could give rise to the need for distinct reaction conditions and catalysts for enantioselective coupling. Previous experiments on cyclic nonfluorinated enolates suggested that the ring size strongly influences enantioselectivity. Both our group[14] and the Buchwald group[15] have found that reactions of 2-methylcyclopentanone and 2-methylcyclohexanone derivatives catalyzed by Pd and Ni complexes of bisphosphine ligands, such as BINAP and Segphos, occurred with much different (and unpredictable) reactivity and enantioselectivity. In separate examples reported by the Zhou group,[16] two different monophosphines on palladium were used to achieve the enantioselective α-arylation and α-vinylation of γ-butyrolactone and δ-valerolactone, thus forming products containing α-tertiary stereocenters in high yields and ee's.

The set of chiral ligands we surveyed for the α-arylation of α-fluoroketones included commercially available monophosphine and bisphosphine ligands, as well as some novel monophosphine ligands derived from BINOL (Scheme 2). The syntheses of the new monophosphines mirrored the syntheses of ligands previously reported by Hayashi[17] and Buchwald,[18] as well as of ligands (*R*)-**L1**−**L3**, previously reported by Zhou

Scheme 2. Monophosphine Ligands (*R*)-L1−L6 That Were Evaluated for the α-Arylation of α-Fluoroketones

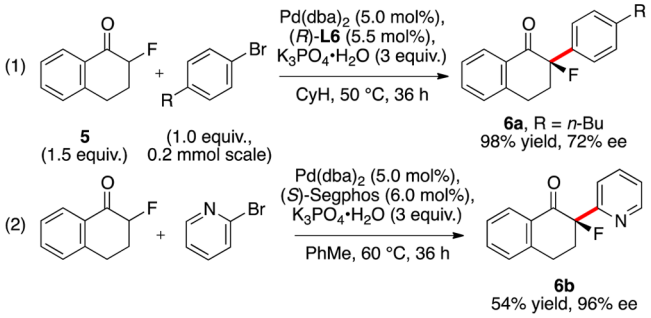


DOI: 10.1021/jacs.6b09580
J. Am. Chem. Soc. 2016, 138, 15980−15986

(Scheme 2a).[16,19] The new ligands contained 1-naphthylmethyl substituents on oxygen and cycloalkyl groups of varying size on phosphorus. Parallel syntheses of these new monophosphine ligands were achieved in four steps from the bis-triflate of (*R*)-BINOL (**1**) and dicycloalkyl phosphine oxides **2a**–**2c**, as shown in Scheme 2b. Selective monophosphination of bis-triflate **1** was followed by hydrolysis of monotriflates **3a**–**3c**, *O*-alkylation of the resultant naphthols with 1-(bromomethyl)-naphthalene, and reduction of phosphine oxides **4a**–**4c** to provide monophosphines (*R*)-**L4**–**L6** in good overall yield (34–57%).

1. Coupling of 2-Fluorotetralones. On the basis of our prior work on the enantioselective α-arylation of α-substituted tetralones,[14] we initially studied the direct coupling of α-fluorotetralones with aryl halides and triflates. We evaluated palladium complexes containing a series of chiral phosphine ligands, and several bases of varying strength and solubility. Details of these experiments are provided in the Supporting Information (SI), Table S5. Ultimately, we found that direct coupling reactions of 2-fluoro-1-tetralone (**5**) with bromoarenes catalyzed by palladium complexes of monophosphine ligands **L4**–**L6** proceeded in high yields but with moderate enantioselectivities. For example, the palladium catalyst generated from ligand **L6** produced tetralone product **6a** from 2-fluorotetralone and 4-butylbromobenzene in 98% yield, but only 72% ee (Scheme 3, eq 1). In contrast, the direct

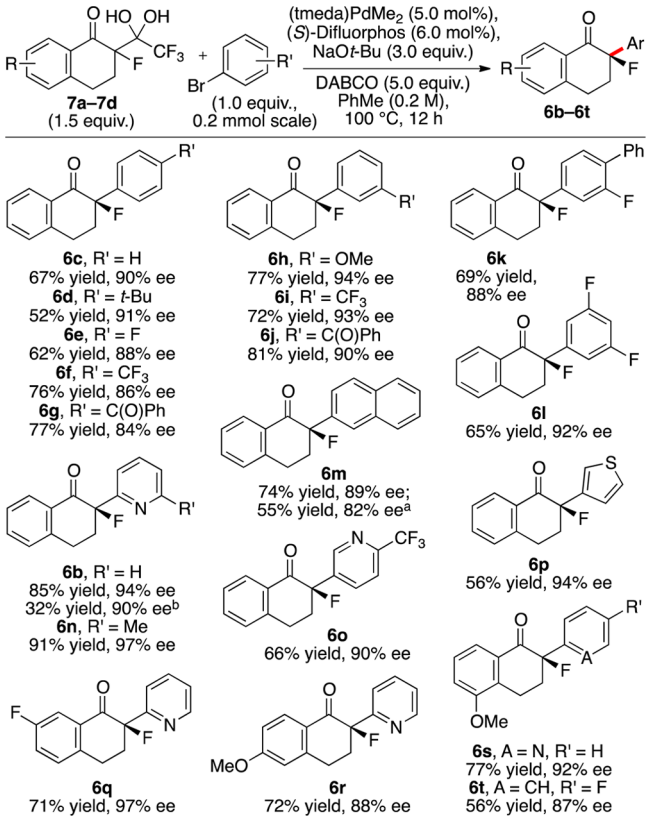
Scheme 3. Direct α-Arylation Reactions of 2-Fluorotetralone



coupling of 2-fluoro-1-tetralone (**5**) with bromopyridines catalyzed by palladium complexes of either (*S*)-Segphos or (*S*)-Difluorphos proceeded with excellent enantioselectivities but in poor to moderate yields. For example, the system generated from (*S*)-Segphos and $Pd(dba)_2$ catalyzed the coupling of α-fluoroketone **5** and 2-bromopyridine to give tetralone product **6b** in 54% yield and 96% ee (Scheme 3, eq 2).

Thus, we sought alternative methods to generate α-fluoro enolates more efficiently and found that reactions in which the enolates are generated from their hydrated, trifluoroacetyl derivatives[7i,20] occurred in higher yields and ee's than the reactions from the ketones directly. Studies of the model reaction between 2-fluoro-1-tetralone **7a** (R = H) and bromobenzene showed that reactions catalyzed by Pd complexes of Segphos and BINAP gave the α-aryl product **6c** in only 75% ee and 37% ee, but the same reaction catalyzed by a combination of $(tmeda)PdMe_2$ and (*S*)-Difluorphos, with NaO*t*-Bu as base and added DABCO in toluene at 100 °C gave ketone **6c** in 67% yield and 90% ee (Scheme 4). As detailed in the SI, Table S1, reactions mediated by weaker bases, such as K_3PO_4, $K_3PO_4·H_2O$, and Cs_2CO_3, converted tetralone

Scheme 4. Scope of Bromoarenes That Couple with Tetralones 7a–7d As Catalyzed by the Pd Complex of (*S*)-Difluorphos



[a]Reaction of 2-naphthyl triflate (0.20 mmol). [b]Reaction of 2-chloropyridine (0.20 mmol).

derivative **7a** to the α-aryl ketone **6c** in low yields (7–20%). Reactions mediated by LiO*t*-Bu and KO*t*-Bu resulted in significant levels of protodefluorination of the intermediate α-fluoro enolate and gave 1-tetralone as the major product (67–90% yield). The identity of the palladium precursor also strongly affected the yield of ketone **6c** (SI, Table S1). Like $(tmeda)PdMe_2$, $Pd(OAc)_2$ is known to release Pd(0) species under catalytic conditions, but reactions conducted with $Pd(OAc)_2$ as precursor gave the coupled product in only 51% yield. Palladium sources containing dba were even less effective catalyst precursors. The addition of 5 equiv of DABCO to the reaction with NaO*t*-Bu as base was also important to producing ketone **6c** in high yield and ee (SI, Table S4). Reaction with fewer equivalents of DABCO or reactions with other alkylamines, such as TMEDA, in place of DABCO resulted in lower yields of the coupled product but similar levels of enantioselectivity (80–90% ee). Finally, experiments indicated that the combination of Difluorphos ligand (SI, Table S2) and a nonpolar solvent, such as toluene (SI, Table S3), was also necessary to obtain high ee's.

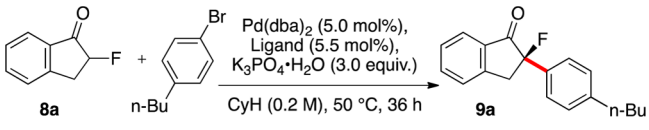
Scheme 4 summarizes the scope of bromoarenes that coupled with trifluoroacetyl derivatives (**7a**–**7d**) of 2-fluoro-1-tetralone under these conditions. In general, reactions of electron-poor aryl bromides gave products (**6e**–**6l**) in higher yields than did reactions of electron-neutral and electron-rich aryl bromides (**6c** and **6d**). A selection of heteroaryl halides derived from pyridine (**6b**, **6n**, and **6o**) and thiophene (**6p**) were suitable substrates. The coupling of tetralone **7a** with

DOI: 10.1021/jacs.6b09580
J. Am. Chem. Soc. 2016, 138, 15980–15986

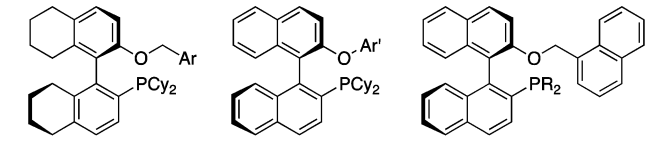
either 2-naphthyl bromide or triflate formed α-aryl product **6m** in high ee (82−89% ee). The reaction of tetralone **7a** with iodobenzene occurred in low yield and ee. The reactions of aryl iodides with (nonfluorinated) 2-methyl-1-tetralone in prior work also occurred in low yield and ee.[14a] Finally, tetralones containing substituents imparting distinct electronic properties to the aryl ring all reacted in high yield and enantioselectivity (**6q**−**6t**).

2. Coupling of 2-Fluoroindanone. To assess the scope of the α-arylation of cyclic α-fluoroketones we also studied the coupling of α-fluoro-1-indanone (**8a**) with 4-butylbromobenzene. In contrast to reactions of 2-fluorotetralone (**5**), the direct catalytic reactions of 2-fluoroindanone **8a** with aryl halides and base occurred in good yield and ee. Reactions catalyzed by palladium complexes generated *in situ* from $Pd(dba)_2$ and a variety of chiral ligands are summarized in Table 1. Catalysts

Table 1. Effect of Ligand on α-Arylation Yield and Enantiomeric Excess



Entry	Ligand[a]	% yield	% ee[b]	Entry	Ligand[a]	% yield	% ee[b]
1	(*S*)-BINAP[c]	2	60	6	**L2**	90	48
2	(*S*)-Segphos[c]	2	23	7	**L3**	92	40
3	(*S*)-Difluorphos[c]	10	62	8	**L4**	95	86
4	(*R*)-MOP	63	38	9	**L5**	94	88
5	**L1**	97	16	10	**L6**	95	89



(*R*)-**L1**: Ar = 2-Naphthyl, (*R*)-**L2**: Ar = 3,5-BTFM-Phenyl; (*R*)-**L3**: Ar' = 2-Naphthyl; (*R*)-**L4**: R = Cyclopentyl, (*R*)-**L5**: R = Cyclohexyl, (*R*)-**L6**: R = Cycloheptyl

[a]Reaction of 1.0 equiv of bromoarene and 1.5 equiv of ketone. [b]Determined by SFC analysis. [c]6.0 mol % ligand at 65 °C.

generated from the bisphosphine ligands (*S*)-BINAP, (*S*)-Segphos, and (*S*)-Difluorphos, which are known to enable enantioselective α-arylation reactions of 2-methyl-1-indanones with high selectivities,[14] produced ketone **9a** in low yields and ee's (23−62% ee, entries 1−3). Catalysts generated from the monophosphines (*R*)-MOP or (*R*)-**L1**−**L3**, the latter of which have been used for enantioselective α-arylations of nonfluorinated esters and cyclic ketones,[16,19] produced ketone **9a** in good yields, but the ee's of these reactions were modest (entries 4−7).

To improve the enantioselectivity of the catalysts containing **L1**−**L3**, while maintaining their high reactivity, we prepared monophosphines **L4**−**L6** that are derived from (*R*)-BINOL and contain 1-naphthylmethyl ether substituents. Catalysts bound by **L4**−**L6** produced ketone **9a** in excellent yields and with greater than 86% ee (entries 8−10). The yields and ee's of reactions of α-fluoroindanone **8a** catalyzed by complexes of **L4**−**L6** were higher than those from reactions catalyzed by complexes of all other monophosphines evaluated in this study. The 1-naphthylmethyl ether side chain of **L4**−**L6** might interact more strongly with the Pd-bound enolate or aryl group than the corresponding ether side chains of **L1**−**L3**. We also observed a subtle, yet direct, relationship between enantioselectivity of the reaction and the size of the cycloalkyl groups on phosphorus: the ee values followed the trend dicyclopentyl (**L4**) < dicyclohexyl (**L5**) < dicycloheptyl (**L6**).

The effects of the Pd precursor, solvent, base, and ratios of coupling partners were small, and the specific data from these experiments are provided in the SI. In brief, the reactions run with $Pd_2(dba)_3$, $[Pd(allyl)Cl]_2$, $[Pd(1\text{-}t\text{-}Bu\text{-}indenyl)Cl]_2$, and $Pd(OAc)_2$ afforded the product in yields and enantioselectivities that were as high as those from reactions run with $Pd(dba)_2$, and reactions run in toluene and ethereal solvents gave the coupled product with ee values that were lower than those of the analogous reaction in cyclohexane, but the difference in ee was only 2−6%. Reactions conducted with 0.2 mmol of indanone **8a** as limiting reagent produced lower isolated yields of α-arylated product **9a** than did the analogous reaction conducted with the aryl bromide as limiting reagent.

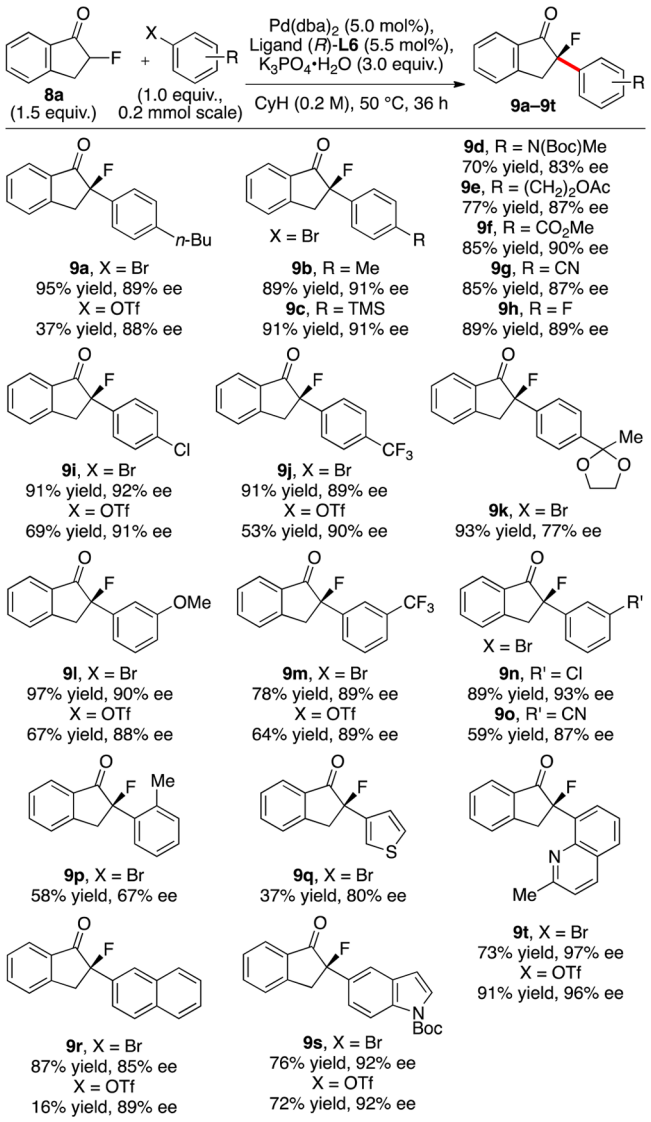
The results of experiments to reveal the effect of base underscore the importance of developing an appropriate method to generate the enolate with rates that are sufficient for catalysis and without creating high concentrations of the alkali metal enolate that facilitate decomposition by protodefluorination. Most striking, the analogous reaction with NaO*t*Bu as base, which was used most commonly for the coupling of nonfluorinated enolates, led to protodefluorination of ketone **8a** as the main product. We suggest that the combination of insoluble bases and hydrocarbon solvents produce potassium fluoro enolates in low concentrations, ensuring that they are efficiently captured by arylpalladium bromide complexes via transmetalation. On a more empirical note, we also found that reactions conducted with weak anhydrous bases, such as Cs_2CO_3 and K_3PO_4, resulted in product yields that were lower than those with hydrated $K_3PO_4{\cdot}H_2O$.

Scheme 5 summarizes the scope of aryl bromides that undergo asymmetric α-arylation with 2-fluoro-1-indanone (**8a**) under the conditions of entry 10 of Table 1. The electronic properties of the aryl bromides had little influence on the yields and enantioselectivities. The reactions of aryl bromides bearing electron-donating (**9a**−**9e** and **9k**) and electron-withdrawing (**9f**−**9j**) substituents in the *para* position formed the coupled products in high isolated yields and ee's. Reactions of *meta*-substituted aryl bromides (**9l**−**9o**) and 2-bromonaphthalene (**9r**) also occurred in good yields and ee's. The reaction tolerates carbamate, silane, acetal, aryl chloride, ester, trifluoromethyl, cyano, and ether functional groups. The coupling also occurred with 2-bromotoluene (**9p**) and 3-bromothiophene (**9q**), but the yields and ee's were moderate. Heteroarylated products formed from the reactions of a 5-bromoindole (**9s**) and 8-bromoquinoline (**9t**) were also isolated in high yields and ee's. The absolute configuration of α-arylation product **9g** formed with (*R*)-BINOL-derived monophosphine **L6** was determined to be (*R*) by single-crystal X-ray diffraction.

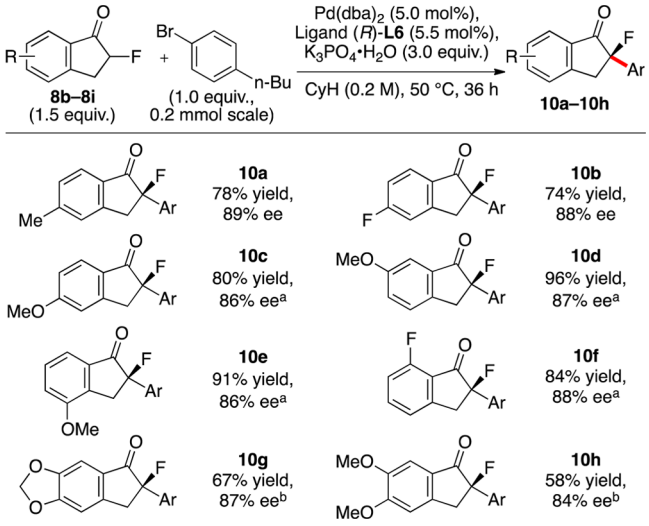
As shown in Scheme 5, the reactions of indanone **8a** with several aryl triflates also were achieved under the conditions of entry 10 in Table 1. The reactions of aryl triflates provided arylated products (**9a**, **9i**, **9j**, **9l**, **9m**, and **9r**−**9t**) with enantioselectivities that are as high as those of the reactions of the corresponding aryl bromides, but in yields that are slightly lower. One exception was the reaction of 2-methyl-8-quinolyl triflate and indanone **8a**, which provided α-arylated product **9t** in 91% yield and 96% ee. The reaction of 8-bromo-2-methylquinoline and the same ketone provided **9t** in 97% ee, but only 73% yield.

DOI: 10.1021/jacs.6b09580
J. Am. Chem. Soc. 2016, 138, 15980−15986

Scheme 5. Scope of Aryl Bromides and Triflates That Couple with Ketone 8a Catalyzed by the Pd Complex of (*R*)-L6



Scheme 6. Scope of 2-Fluoroindanones That Couple with 4-Bromobutylbenzene Catalyzed by the Pd Complex of (*R*)-L6



[a]Reaction in 2:1 CPME:CyH. [b]Reaction in CPME.

Scheme 6 summarizes the scope of 2-fluoro-1-indanones that undergo the asymmetric α-arylation. 2-Fluoroindanones bearing electron-donating and moderately electron-withdrawing groups underwent this cross coupling in high yields and enantioselectivities (**10a** and **10b**). However, in some cases, poor solubility of the indanone in cyclohexane led to low yields. In these cases, the reactions with added cyclopentyl methyl ether (CPME) occurred in higher yield but slightly lower ee (**10c**–**10h**) than did those without CPME. The results of these experiments are shown in the SI, Table S11. Methoxy substituents at the 4-, 5-, and 6-positions of the indanone had little impact on the yield and enantioselectivity of the reaction (**10c**–**10e**). The indanone containing a methoxy substituent at the 7-position did not react, but one containing a smaller fluorine atom at the 7-position reacted in good yield and ee (**10f**).

Having identified conditions for the enantioselective α-arylation of 2-fluoro-1-indanones, we investigated the coupling of these ketones with pyridine-based electrophiles. Reactions of ketone enolates with halopyridines are challenging because the Lewis basic nitrogen atom can bind to the metal and poison the catalyst or alter enantioselectivity, particularly when the catalyst is bound by a hindered monophosphine. Indeed, the reaction of 2-bromopyridine and ketone **8a** catalyzed by palladium bound by monophosphine **L6** did not give coupled product. However, the same reaction catalyzed by $Pd(dba)_2$ and the bisphosphine (*S*)-Segphos in toluene at 65 °C gave the α-fluoro-α-heteroaryl product **9u** in 98% yield and 91% ee (Scheme 7).

Scheme 7 summarizes the scope of heteroaryl and electron-deficient aryl electrophiles that react with 2-fluoro-1-indanones in the presence of $Pd(dba)_2$ and (*S*)-Segphos. The reaction of 2-fluoro-1-indanone (**8a**, R = H) and 2-pyridyl electrophiles gave product **9u** in consistently high ee (91–94% ee), but the reactions of 2-bromo- and 2-chloropyridine gave this product in yields that were higher than that of the corresponding reaction of 2-pyridyl triflate. The reaction of indanone **8a** with 2-bromo-6-methylpyridine also proceeded in high yield and enantioselectivity at 65 °C (**9v**), but the direct coupling of the same indanone with a 3-bromopyridine proceeded in good yield and high ee at 90 °C (**9w**).

The strategy of generating enolates by elimination of trifluoroacetate was also evaluated for the enantioselective coupling of 2-fluoroindanones to determine if the yields and enantioselectivities would be even higher for reactions of these precursors. Several aryl and heteroaryl electrophiles reacted in the presence of Pd catalysts ligated by Segphos to give α-aryl-α-fluoroindanone products in high yields and ee's. However, these data largely parallel the values reported in Scheme 7 and are provided in the SI.

To understand the relationship between the reactions of the indanone conducted by direct deprotonation of the ketone and by elimination of trifluoroacetate from the trifluoracetate adduct, the reaction of the trifluoracetate adduct of 2-fluoroindanone **11a** and 2-bromopyridine was monitored by ^{19}F NMR spectroscopy. In the presence of a 2-fold excess of $K_3PO_4{\cdot}H_2O$, we observed that adduct **11a** reacted within 2 h at 23 °C to form 2-fluoroindanone **8a** in 95% yield (eq 3). This result indicated that the dominant species generated from elimination of trifluoroacetate in the presence of $K_3PO_4{\cdot}H_2O$ was the neutral α-fluoroindanone, not the corresponding

DOI: 10.1021/jacs.6b09580
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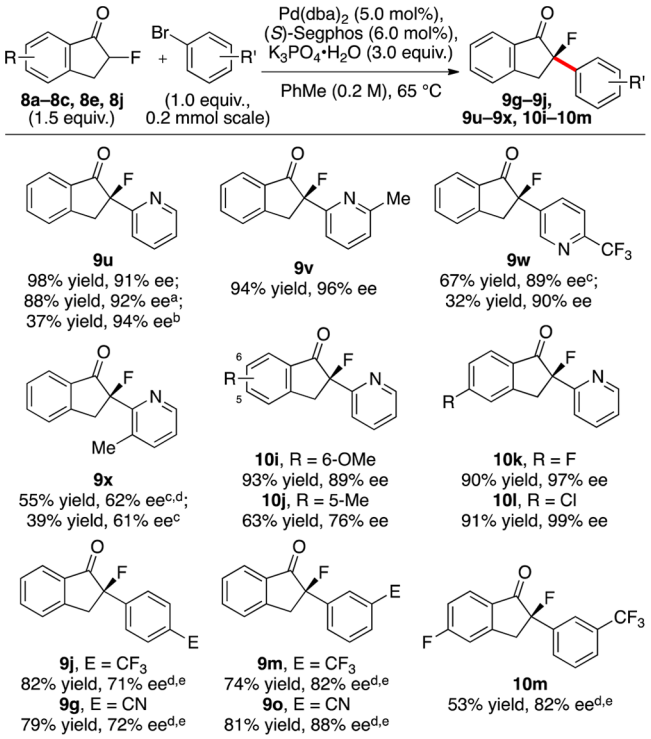
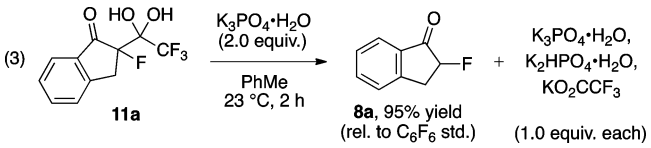
Scheme 7. Scope of (Hetero)aryl Bromides That Couple with 2-Fluoroindanones Catalyzed by the Pd Complex of (*S*)-Segphos



[a]Reaction of 2-chloropyridine (0.20 mmol). [b]Reaction of 2-pyridyl triflate (0.20 mmol). [c]Reaction at 90 °C. [d]Reaction with 0.5 equiv of CF_3CO_2K added. [e]Reaction at 80 °C with anhydrous K_3PO_4 (3.0 equiv) as base.



anionic α-fluoro enolate. The neutral α-fluoroindanone was also the major species observed during the reaction of 2-bromopyridine and ketone **8a** that forms product **9u**, which proceeds by direct deprotonation of the ketone by $K_3PO_4{\cdot}H_2O$ base. In contrast, both breakdown of indanone adduct **11a** in the presence of NaO*t*-Bu, and direct deprotonation of ketone **8a** by NaO*t*-Bu, resulted in their complete conversion to 1-indanone, presumably by protodefluorination of the corresponding sodium enolates. These results reveal the instability of the enolate of indanone **8a** toward side reactions that are avoided by generating them in low concentrations during catalysis.[21]

By stoichiometry, the reaction shown in eq 3 should also form 1 equiv of potassium trifluoroacetate and potassium biphosphate, with 1 equiv of the phosphate base remaining. This breakdown of adduct **11a** and release of trifluoroacetate occurred prior to addition of 2-bromopyridine, Segphos, and $Pd(dba)_2$. Because this reaction generated the same ketone as is used in the direct coupling, but with 1 equiv of trifluoroacetate, we assessed whether the direct α-heteroarylation of 2-fluoroindanone **8a** would be affected by the addition of trifluoroacetate.

To do so, we ran several of the examples in Scheme 7 in the presence of potassium trifluoroacetate. The reactions that formed products **9u**–**9w** and **10i**–**10l** were not affected by the presence of potassium trifluoroacetate. However, the reaction of sterically hindered 2-bromo-3-methylpyridine catalyzed by the palladium complex of (*S*)-Segphos in the absence of the acetate gave **9x** in low yield, whereas the same reaction with 0.5 equiv of CF_3CO_2K occurred in higher yield and approximately the same ee. We speculate that the yield is higher with added CF_3CO_2K because this base facilitates the formation of a Pd-enolate complex.

These conditions with added CF_3CO_2K also allowed couplings of fluoroindanones with electron-poor heteroarenes to occur in high yields and good enantioselectivities with commercially available Segphos to supplement the reactions run with monophosphine ligand **L6**. The reactions of α-fluoroindanone **8a** with trifluoromethyl- and cyano-substituted bromoarenes conducted with 0.5 equiv of added CF_3CO_2K gave higher yields of α-arylated products **9g**, **9j**, **9m**, **9o**, and **10m** than did the reactions conducted without CF_3CO_2K by as much as 31% and similar levels of enantioselectivity. We also found that these reactions gave the product in high yields and consistently higher ee's with anhydrous K_3PO_4 as base than with $K_3PO_4{\cdot}H_2O$. The results of these reactions with anhydrous K_3PO_4 base are shown in Scheme 7, whereas the results from those reactions involving hydrated phosphate base have been provided in the SI, Table S12.

The α-heteroarylation of substituted α-fluoroindanones also occurred. In these cases, Pd complexes of (*S*)-Segphos catalyzed the formation of ketones **10i**–**10l** in good yields and ee's at 65 °C without added trifluoroacetate. It is worth noting that the reaction of 5-chloro-2-fluoroindanone gave product **10l** in 91% yield and 99% ee without detectable functionalization of the C–Cl bond. Overall, these results demonstrate the complementarity of palladium catalysts ligated by monophosphine ligand **L6**, which directly coupled 2-fluoroindanones with aryl bromides and triflates in high yields and ee's, and catalysts ligated by Segphos, which coupled the same ketones with Lewis basic bromoheteroarenes and electron-deficient bromoarenes in high yields and ee's.

CONCLUSION

In this work we show that chiral α-fluoroketones containing fully substituted carbons bearing fluorine can be generated enantioselectively by carbon–carbon bond formation. The reactions of indanones with aryl and heteroaryl bromides and triflates occur in high yields and ee's with palladium catalysts ligated by the monophosphine **L6** and the bisphosphine Segphos. The reactions of tetralones rely on the elimination of trifluoroacetate to release α-fluoro enolates and a palladium catalyst complexed by Difluorphos.

These results underscore the effect of fluorine on the acidity and nucleophilicity of carbonyl compounds. No single catalyst system or single set of conditions leads to the enantioselective coupling of a wide range of enolates, and the reactions of the fluorinated enolates are no exception. Nevertheless the family of catalysts we report here, in combination with the methods for generating the fluorinated enolates in other contexts applied to α-arylation provide a foundation for future studies on these new classes of reactions. Clearly, the design of more general systems will require a greater understanding of the factors controlling the yield and enantioselectivity, and efforts to generate discrete fluoro enolate complexes of palladium that

DOI: 10.1021/jacs.6b09580
J. Am. Chem. Soc. 2016, 138, 15980–15986

would provide a direct view into the factors controlling the formation and reaction of fluorinated enolate complexes in these processes are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09580

X-ray crystallographic data for **S1** (CIF)
X-ray crystallographic data for **9g** (CIF)
Experimental procedures and spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Singapore Ministry of Education Academic Research Fund (MOE2013-T2-2-057, MOE2014-T1-001-021), the NIH (F32GM106641 for J.J.B.), the Kyushu University Program for Leading Graduate Schools (Y.J.), and the NSF (CHE-1565886) for financial support. We thank Yicheng Weng for preliminary data on the reactions of fluorinated ketones.

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(21) We also generated the sodium enolate of tetralone **5** by direct deprotonation with NaO*t*-Bu, and by elimination of trifluoroacetate from adduct **7a** in the presence of NaO*t*-Bu. Both methods for forming this enolate generate species that have identical ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts. However, catalytic reactions of this enolate generated by these two methods do not give the same yields and ee values for the coupled products. We do not yet understand the origin of this difference.

DOI: 10.1021/jacs.6b09580
J. Am. Chem. Soc. 2016, 138, 15980−15986