

Palladium-Catalyzed Arylation of Trimethylsilyl Enolates of Esters and Imides. High Functional Group Tolerance and Stereoselective Synthesis of α -Aryl Carboxylic Acid Derivatives

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Abstract: A general procedure for the palladium-catalyzed arylation of trimethylsilyl enolates of esters and imides is reported. In the presence of ZnF_2 or $\text{Zn}(\text{O}-t\text{-Bu})_2$ as an additive, the trimethylsilyl enolates of esters, including those bearing α -alkoxy derivatives, underwent arylation in high yield with high functional group tolerance. This arylation chemistry was extended to ester derivatives bearing chiral auxiliaries to form new tertiary stereocenters. The arylation of imides bearing the Evans auxiliary proceeded with selectivities up to 90% de. Further, the arylation of the ketal developed by Ley provided α -aryl glycolates with excellent diastereoselectivities (90 to >98% de). This reaction provides a convenient route to the synthesis of enantiopure α -aryl- α -hydroxy esters. Reactions conducted with $\text{Zn}(\text{O}-t\text{-Bu})_2$ as an additive occurred at room temperature to give enhanced diastereoselectivities with both chiral reagents. Mechanistic studies showed that the reaction conditions are neutral enough that the observed diastereomeric ratios reflect kinetic selectivities.

Introduction

The reaction of an electrophile with an enolate is a fundamental organic transformation. Though the scope of uncatalyzed reactions of enolates with alkyl halide electrophiles is broad, the scope of similar reactions of enolates with aryl halides is limited. Much effort has been spent to render the arylations of enolates as general as alkylations. Some progress has been made with main group arylating reagents such as organobismuth and aryllead compounds.^{1–5} However, the arylations of enolates became more general with the recent development of palladium-catalyzed procedures^{6–8} for the α -arylation of ketones,^{9–12} esters^{13–18} and amides.^{19,20}

Although mild in temperature and efficient in catalyst loadings,^{15,18} these reactions are constrained by the stability and functional group tolerance of alkali metal enolates at room temperature and above. Because the enolate must be stable enough to resist decomposition and condensation on the time scale of the catalytic chemistry, the arylation of esters^{15,18} has been limited to enolates such as those of *tert*-butyl acetate, *tert*-butyl propionate, or methyl isobutyrate that are stable at room temperature.^{21,22} Moreover, other functional groups contained in the coupling partners must be stable to the basic medium at room temperature or above. Palladium-catalyzed reactions of alkali metal enolates of esters with aryl halides that contain highly electrophilic functionality such as acetyl and nitro groups have not been reported. Finally, products from reactions of aryl halides with alkali metal enolates that possess new tertiary stereocenters and reagents that contain remote stereocenters that are sensitive to base are likely to undergo racemization in the presence of the alkali metal enolates.^{23,24} Thus, more neutral reaction conditions would expand the scope and applications of the palladium-catalyzed arylation of enolates.^{25,26}

We have recently investigated reactions of trimethylsilyl enolates and zinc enolates. Reactions of Reformatsky reagents^{25,26} with aryl halides occurred with broader scope than

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reactions of alkali metal enolates, but certain functionalities remained intolerant of the conditions, and *tert*-butyl esters were required to observe clean reactivity from acetate and propionate Reformatsky reagents. If the silyl enolates reacted on their own under palladium-catalyzed conditions or with an additive that did not simply generate high concentrations of alkali metal enolates, then reactions of these reagents would be expected to show high functional group tolerance. Moreover, trimethylsilyl enolates can be synthesized directly from esters or amides and are relatively stable to air and moisture.

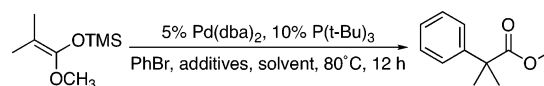
Previously, palladium-catalyzed coupling of these reagents was reported in the presence of stoichiometric amounts of tin fluoride additive to generate the tin enolates^{27,28} or in the presence of suprastochiometric amounts of copper fluoride²⁹ under conditions that involved an excess of enolate with respect to aryl halide. Both of these protocols have drawbacks. Tin halides are toxic, and only the acetate enolate was shown to be reactive in the presence of the copper fluoride additive. One specific case of the reaction of an activated aryl triflate with a silyl ketene acetal in the presence of ZnCl₂ additive has been reported.³⁰

Considering the many reports of Lewis acid-promoted aldol reactions of trimethylsilyl ketene acetals,³¹ we evaluated reactions of the combination silicon enolates and Lewis acidic reagents to observe the coupling of this type of enolate. We recently reported preliminary results on the arylation of trimethylsilyl ketene acetals.²⁶ Herein, we report the discovery of two zinc additives that allow palladium complexes to catalyze the arylation of trimethylsilyl enolates and the use of these additives with enolates bearing chiral auxiliaries to form optically active α -aryl carboxylic acid derivatives.

Results and Discussion

Reactions of trimethylsilyl ketene acetal with phenyl bromide in the presence and absence of various additives are summarized in Table 1. Reactions of trimethylsilyl ketene acetal and PhBr in dioxane in the presence of Pd(dba)₂ and P(*t*-Bu)₃ as catalysts at 100 °C for 12 h without additive led to no product. The same reaction in DMF at 80 °C occurred to partial completion. Reactions of these substrates with mild Lewis acids such as ZnCl₂ and CuCl in dioxane or DME in the presence of Pd(dba)₂ and P(*t*-Bu)₃ as catalyst at the same temperatures and times gave no product, as determined by GC. However, reactions with 0.5 equiv of ZnF₂ as an additive at 80 °C in DMF solvent in the presence of the combination of Pd(dba)₂ and P(*t*-Bu)₃ as catalyst led to reaction of the trimethylsilyl ketene acetal with PhBr. Reaction with 0.25 equiv of ZnF₂ also occurred to completion and formed the coupled product in 93% yield as determined by GC. This result suggests that ZnF₂ serves as a cocatalyst rather than a stoichiometric reagent. Interestingly, 1.0 equiv of LiCl also promoted reaction with the same catalyst, but only about 80% of the PhBr was converted to product after 12 h at 80 °C in this case.

Table 1. Effect of Additives on the Arylation of Trimethylsilyl Ketene Acetal



entry	additives	solvent	product:ArBr ^a	yield ^b
1	none	dioxane	0:100	0% ^{c,d}
2	none	DMF	24:76	nd
3	ZnCl ₂	dioxane	0:100	0% ^{c,d}
4	CuCl	dioxane	0:100	0% ^{c,d}
5	ZnCl ₂ (0.5 equiv)	DME	0:100	0%
6	ZnCl ₂ (0.5 equiv)	DMF/DME (1:1)	44:56	nd
7	ZnCl ₂ (0.25 equiv)	DMF/DME (1:1)	75:25	66%
8	ZnBr ₂ (0.25 equiv)	DMF/DME (1:1)	49:51	38%
9	ZnF ₂ (0.5 equiv)	DMF/DME (1:1)	97:3	95%
10	ZnF₂ (0.5 equiv)	DMF	100:0	~100%
11	ZnF₂ (0.25 equiv)	DMF	100:0	93%
12	LiCl (1.0 equiv)	DMF	83:17	nd

^a Determined by GC. ^b GC yield; nd = not determined. ^c *p*-Butyl-PhBr was used. ^d *T* = 100 °C.

The scope of the arylation of silyl ketene acetals with aryl bromides in the presence of 0.5 equiv of ZnF₂ as a cocatalyst and the combination of P(dba)₂ and P(*t*-Bu)₃ as catalyst is illustrated in Table 2. Reaction of 1.5 equiv of the trimethylsilyl ketene acetal with PhBr in the presence of 0.5 equiv of ZnF₂ and 1 mol % palladium catalyst in DMF at 80 °C generated the coupled product in 91% isolated yield (entry 1). Most important, these reactions occurred in similarly high yields with aryl bromides that contain a variety of functional groups not tolerated by the coupling of alkali metal enolates.

For example, 4-bromonitrobenzene reacted with the silyl ketene acetal of methyl isobutyrate and methyl propionate to give the arylated products in 98% (entry 2) and 76% yield (entry 3). Ester and (entries 4, 5) nitrile (entries 6, 7) functionalities were also compatible with the conditions for coupling of silicon enolates in the presence of zinc additive. Different substitution patterns on the aryl bromide were tolerated; both 2-cyano- (entry 6) and 3-cyanobromobenzene (entry 7) reacted with the silyl ketene acetal of methyl propionate to give the arylated product in 75 and 67% yields, respectively. Bromobenzophenone reacted with the enolate of methyl isobutyrate in 95% yield (entry 8). In contrast to reactions of alkali metal and zinc enolates, 4-bromoacetophenone reacted with the silyl enolates of methyl isobutyrate and *tert*-butyl propionate (entries 9, 10) to provide the coupled products in high yield. These results suggest that the activated main group enolate undergoes transmetalation with the palladium intermediate faster than potential nucleophilic attack on the ketone and enolization of the acidic proton. Electron-rich aryl bromides (entry 11) also underwent the coupling reaction in high yield.

The scope of reactions of chloroarenes with the silicon enolates was narrower than that of reactions of bromoarenes, and higher catalyst loadings were required. As shown in Table 2, activated chloroarenes such as *p*-chloro nitrobenzene (entry 12) and *p*-chloro methylbenzoate (entry 13) coupled with the trimethylsilyl ketene acetal to provide the desired product in excellent yields in the presence of 5 mol % catalyst.

α -Arylation of Imides Bearing the Evans Auxiliary.

Encouraged by the success of the arylation of the silyl enolates of simple esters, we sought to extend this methodology to reactions of enolates that would exploit further the low basicity

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Table 2. Coupling of Silylketene Acetals with Aryl Halides

entry	ArX	trimethylsilyl enolate	product	yield ^a
1				91%
2				98%
3				76%
4				94%
5				80%
6				75%
7				67%
8				99%
9				78%
10				68%
11				88%
12 ^b				95%
13 ^b				96%

^a Isolated yields of reactions on 1.0 mmol scale. Values are an average of two runs. ^b Performed with 5% catalyst.

of the reaction medium. Carboxylic acid derivatives bearing chiral auxiliaries are often used to prepare optically active carbonyl derivatives.^{32–35} α -Arylation and subsequent cleavage of the auxiliary would provide an enantioselective synthesis of α -aryl carbonyl compounds.

Such a reaction sequence initiated with alkali metal enolates would be limited in two ways. First, many of the alkali metal enolates of ester derivatives bearing common auxiliaries are unstable at the temperatures required for catalysis. Second, the arylated product is more acidic than the reactant, and a base that is strong enough to generate the enolate would epimerize

the α -stereocenter of the product. Thus, the reactions must be conducted under conditions that do not generate alkali metal enolate and that are neutral enough to prevent epimerization of the α -stereocenter of the product. The conditions for the α -arylation of silicon enolates with zinc additives seemed likely to fit these criteria.

Among many chiral auxiliaries available for controlling the stereochemistry of ester derivatives,^{32–35} the Evans auxiliary³² was chosen for initial study. The products that would result from this arylation process are capable of being readily transformed into carboxylic esters, ketones, aldehydes, and alcohols by known methods.^{32,36–38} Results from arylation of enolates bearing the Evans auxiliary are presented in Table 3. Heating of the trimethylsilyl enolate of the Evans auxiliary with PhBr in DMF at 80 °C in the presence of ZnF₂ and the combination of 5% Pd(dba)₂ and 10% P(^tBu)₃ led to formation of the diastereomeric coupled products in an 88:12 ratio. The major

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Table 3. Diastereoselective Reactions of Silyl Ketenimides Bearing the Evans Auxiliary with Aryl Bromides

entries	product ^a	zinc additives	T	yield ^b	d.r. ^c
1		ZnF ₂	80 °C	67%	87:13
2		Zn(Ot-Bu) ₂ ^d	rt	70%	91:9
3		ZnF ₂	80 °C	58%	92:8
4		Zn(Ot-Bu) ₂ ^d	rt	61%	95:5
5		ZnF ₂	80 °C	75% ^e	84:16
6		ZnF ₂	80 °C	78%	92:8
7		ZnF ₂	80 °C	57%	83:17
8		ZnF ₂	80 °C	65%	77:23
9		ZnF ₂	80 °C	35% ^f	89:11

^a The stereochemistry of the diastereomeric products in entry 1 was established by comparison of the NMR spectra to those of literature values for **3** and *epi-3*. The relative stereochemistry of the other products were established by NMR data that were similar to those of **3** and *epi-3*. ^b Isolated yield of reactions on 0.5 to 1.0 mmol scales; average of two runs. The catalyst loading was not optimized. ^c Determined by integration of crude ¹H NMR spectra. ^d Commercial zinc *t*-butoxide contained roughly 50 wt % water, as determined by NMR spectroscopy. The quantity of Zn(Ot-Bu)₂ added was calculated to be 0.25 equiv, when considering that the commercial material is 50% Zn(Ot-Bu)₂ by weight. ^e Combined yield of two isomers. ^f Yield determined by NMR spectroscopy.

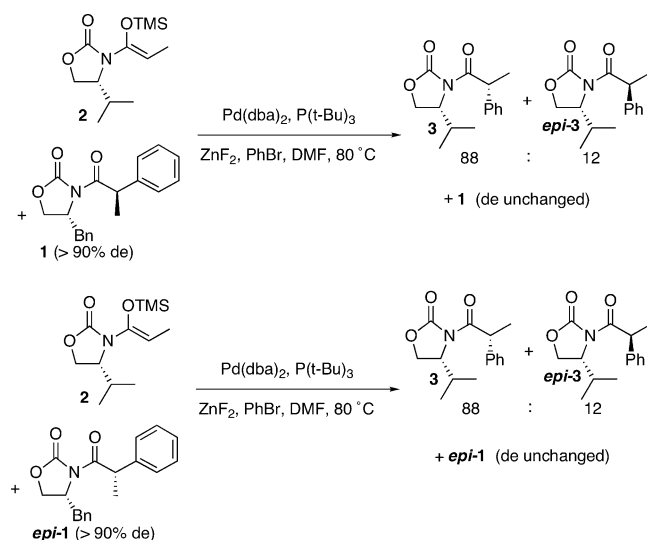
diastereomer was isolated in 67% yield (entry 1). Reaction of the more sterically demanding auxiliary derived from *tert*-leucinol, instead of valinol, formed the diastereomeric products in a 92:8 ratio (entry 3).

The scope of the aryl halide that underwent reaction with this silyl ketenimide was broad. As shown in Table 3, 3-bromoacetophenone (entry 5) coupled with the Evans auxiliary to give the arylated product in 75% yield with a diastereomeric ratio of 84:16. The ortho-substituted *o*-bromotoluene (entry 6), reacted with the silyl enolate to afford the major diastereomer in 78% yield with a diastereomeric ratio of 92:8. The electron-neutral, para-substituted aryl bromide *p*-*t*-butylbromobenzene (entry 7) afforded the major isomer in 57% yield with a diastereomeric ratio of 83:17. The electron-poor 4-cyanophenylbromide (entry 8) reacted to give the major diastereomer in

65% isolated yield. The diastereomeric ratio (77:23) was lower than that obtained with more electron-rich aryl bromides. The more hindered imide bearing a *tert*-butylacetyl group (entry 9) also underwent reaction with phenyl bromide to provide the arylated product with a diastereomeric ratio of 89:11, but a lower 35% yield of the major diastereomer was formed, as determined by NMR spectroscopy.

Variation of the zinc additive led to faster reaction rates and improved diastereoselectivities over those obtained with ZnF₂ as an additive. Reaction of PhBr in the presence of Zn(O-*t*-Bu)₂ with the silyl enolate of the auxiliary derived from valinol occurred at room temperature to generate a ratio of the two diastereomers in the crude reaction mixture of 91:9 (entry 2) and the major diastereomer in 70% isolated yield. The reaction rate may be faster with this zinc additive because it is more

Scheme 1



soluble than ZnF_2 . Reactions of aryl bromides with the imide containing the auxiliary from valinol in the presence of $\text{Zn}(\text{O}^i\text{Bu})_2$ at the higher temperature of 80°C generated slightly lower diastereomeric excess than did reactions in the presence of ZnF_2 at the same temperature. This result indicates that the higher diastereoselectivity results from lower temperatures and not from a direct effect of the zinc additive on the step that controls diastereoselectivity. The faster rates also led to full conversion of PhBr at room temperature upon reaction of the silyl enolate bearing the oxazolidinones from *tert*-leucinol (entry 4). In this case, the diastereoselectivity was 95:5, and the major diastereomer was isolated in 61% yield.

To determine whether the ratio of diastereomers obtained from these reactions was the kinetic ratio, we conducted the arylation of the silicon enolate **2** in the presence of a diastereomerically pure α -aryl imide **1** and in the presence of pure *epi*-**1**. As shown in Scheme 1, the reaction formed the same 88:12 ratio of diastereomers as the reaction conducted without added α -aryl imide. Most important, the α -aryl imides **1** and *epi*-**1** showed no discernible decay of their diastereomeric excess during the reaction. This result clearly shows that the coupling process creates kinetic ratios and that the conditions for the arylation of silicon enolates are neutral enough to prevent the epimerization of the base-sensitive stereocenters.

The origin of diastereoselection of the catalytic arylation of the silicon enolates was different from the origin of diastereoselection of the uncatalyzed alkylation of lithium enolates. If the palladium intermediate were to approach the silicon enolate in the same fashion that an alkyl halide approaches the lithium enolate,^{39,40} then one would expect to obtain *epi*-**3** as the major diastereomer after reductive elimination from palladium with retention of configuration.³² However, diastereomer **3** was the major isomer obtained from the arylation reaction. The formation of the opposite diastereomer to that expected from the geometry of the lithium enolates could result from

reaction of palladium with the (*E*)-silicon enolate instead of the (*Z*)-lithium enolate. Alternatively, the weaker ability of silicon to chelate the carbonyl groups could make the conformation of the silicon enolate that reacts with palladium different from the conformation of the lithium enolates that react with alkyl halides. This conformation may involve a roughly 180° rotation about the C–N bond to place the carbonyl dipoles in opposite directions, and this opposite orientation of the auxiliary would lead to formation of the opposite diastereomer.

α -Arylation of Acyclic α -Alkoxy Esters. Hydroxy or alkoxy esters are important biological compounds,⁴¹ and much effort has been spent to develop methods to prepare them.^{42–47} α -Aryl, α -hydroxy esters are an important subset of these compounds, and their synthesis remains challenging.⁴² We envisioned the α -arylation of a hydroxy ester derivative as a rapid route to these compounds. The success in the diastereoselective arylation of the Evans auxiliary suggested that arylation of an α -hydroxy ester derivative bearing an appropriate chiral auxiliary could create an enantioselective synthesis of α -aryl, α -hydroxy esters.

Because the enolates of α -alkoxy esters decompose at room temperature,^{48,49} attempts to conduct the α -arylation of the alkali metal enolates of α -alkoxy esters were unsuccessful. As shown in Scheme 2, reactions of PhBr with the lithium or sodium enolate of benzyloxyl *tert*-butyl acetate **4** with $\text{Pd}(\text{dba})_2$ as a catalyst and $\text{P}(\text{t-Bu})_3$ or a hindered heterocyclic carbene as the ligand provided the arylated product **5** in less than 20% yield, as determined by GC. The reaction between PhBr and the lithium or sodium enolate of the less hindered methoxy ethyl acetate under similar conditions gave ester **7** in even lower yield (<5%).

Silicon enolates of these esters are more stable thermally. This thermal stability, in combination with a method to induce coupling chemistry from silicon enolates, allowed the development of methods to generate α -aryl, α -alkoxy esters in good yields. Results of the coupling of two representative α -alkoxy esters, benzyloxyl *tert*-butyl acetate **4** and methoxy ethyl acetate **6**, with various aryl halides is summarized in Table 4. Reactions of the silyl enolates **4** and **6** occurred with aryl halides with diverse electronic properties (entries 1–3). Aryl halides, such as 4-bromonitrobenzene (entry 2), that are sensitive to base, as well as aryl halides, such as methyl-4-bromobenzoate (entry 6), that are sensitive to nucleophilic reagents, underwent reaction with the α -alkoxy esters in good yields. Moreover, these reactions occurred with enolates that form products with new quaternary centers (entry 4).

α -Arylation Cyclic Esters Bearing the Ley Auxiliary: Diastereoselective Synthesis of α -Aryl, α -Hydroxy Esters.

With conditions to conduct the arylation of achiral alkoxy esters, we sought to develop arylations of α -alkoxy esters bearing a chiral auxiliary that would allow for a stereoselective synthesis of α -aryl, α -hydroxy esters. Among the auxiliaries that could

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Table 4. Arylation of Silicon Enolates of Alkoxy Esters

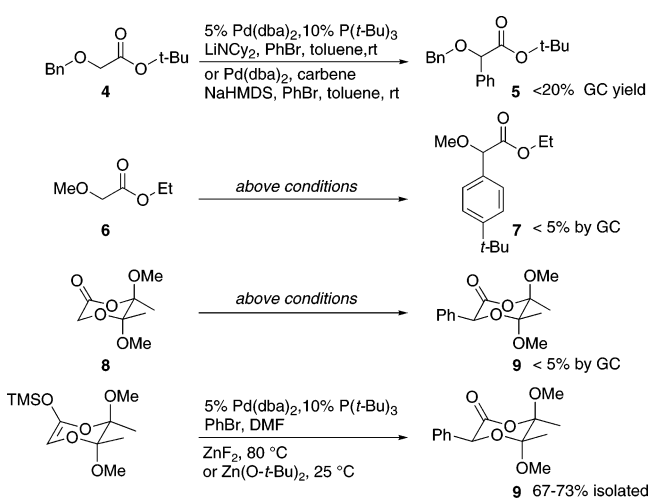
$\text{R}^1\text{O}-\text{C}(\text{OTMS})=\text{C}(\text{R}^2)-\text{OR}^3 + \text{ArBr} \xrightarrow[0.5 \text{ eq ZnF}_2, \text{ DMF, } 80^\circ\text{C, } 12 \text{ h}]{5\% \text{ Pd}(\text{dba})_2, 10\% \text{ P}(t\text{-Bu})_3}$		$\text{R}^1\text{O}-\text{C}(\text{Ar})(\text{R}^2)-\text{OR}^3$	
product	yield ^a	product	yield ^a
1	85%	4	75%
2	79%	5	54%
3	87%	6	63%

^a Isolated yield of reactions on a 1.0 mmol scale, average of two runs.

be suitable for these studies^{44,50} we chose to investigate the cyclic ketal **8** designed by Ley et al.⁴⁴ This auxiliary has been shown previously to undergo highly diastereoselective alkylation and aldol condensation reactions.^{44,51–54} We sought, in part, to compare the diastereoselection of the arylation process with this rigid cyclic structure to that we obtained with the Evans auxiliary.

As shown in Scheme 2, reactions of the dioxanone **8** with aryl bromides in the presence of alkali metal base and the combination of 5 mol % Pd(dba)₂ and 10 mol % P(*t*-Bu)₃ as a catalyst occurred in yields that were as low as those from reactions of acyclic α -alkoxy enolates with aryl bromides. However, the combination of the silicon enolate of **8** and ZnF₂ reacted at 80 °C with phenyl bromide in the presence of Pd(dba)₂ and P(*t*-Bu)₃ as a catalyst to provide the coupled product in good yield and with high diastereoselectivity. Moreover, analogous reactions of aryl bromides with the combination of the silicon enolate of **8** and Zn(O*t*-Bu)₂ occurred at room temperature.

Results on the arylation of the silyl enolate of Ley's dioxanone **8** are summarized in Table 5. Phenyl bromide coupled with this enolate in the presence of 0.5 equiv of ZnF₂ (entry 1) to provide a single diastereomer, as determined by NMR spectroscopy, in 67% isolated yield. Reactions conducted at room temperature with Zn(O*t*-Bu)₂ (entry 2) as an additive also occurred with high diastereoselectivity, and the reaction yields were slightly higher (73%) when this zinc additive was used. The amount of zinc additive influenced the yield of product

Scheme 2

and conversion of the aryl bromide. For example, reactions conducted with 0.5 equiv of Zn(O*t*-Bu)₂ instead of 0.25 equiv afforded 95% instead of 80% yield (entry 5 vs entry 4). This effect of the amount of zinc reagent was observed with reactions of several bromoarenes. Coupling between 3-nitrobromobenzene and the silyl enolate of **8** proceeded in 78% yield with 0.25 equiv of Zn(O*t*-Bu)₂ (entry 6) but occurred in a higher 89% yield in the presence of 0.5 equiv of Zn(O*t*-Bu)₂ (entry 7).

As expected from results of other coupling reactions of silyl enolates, the reaction of the silicon enolate of dioxanone **8** occurred with a variety of electronically and sterically distinct aryl halides, including those containing electrophilic functional groups. Reactions of the electron-rich 4-bromoanisole (entry 9) produced the coupled product in 58% yield with a diastereomeric ratio greater than 50:1. Ortho-substituted aryl bromides also coupled with the silicon enolate of **8** in good yield and with high stereoselectivity (entries 11, 12). Moreover, aryl bromides containing potentially reactive electron-withdrawing groups such as acetyl, nitro, and ester groups, as well as an aryl halide containing a chloro substituent (entries 4, 6, 9, 11), reacted with this enolate with high stereoselectivity. For example, methyl 4-bromobenzoate coupled with a combination of the silyl enolate of **8** and Zn(O*t*-Bu)₂ additive at room temperature to form a single diastereomer by NMR spectroscopy in 80% yield (entry 4). The equally high selectivity of the reactions of the enolate of **8** with activated and unactivated aryl halides contrasts with the lower diastereoselectivities obtained from reactions of the silyl enolate of the Evans auxiliary with activated aryl halides.

Zinc *t*-butoxide from our commercial source contained roughly 50% water by weight. Therefore, the molar amount of zinc is roughly half the amount that would be added if the reagent contained only zinc *tert*-butoxide. Thus, a reaction conducted with 0.5 equiv of zinc *tert*-butoxide that was dried by refluxing in benzene with a Dean–Stark apparatus gave the coupled product in a yield determined by NMR spectroscopy that was comparable to that obtained with twice the amount of the commercial “zinc *tert*-butoxide”. Because this reaction tolerated the presence of water, a reaction conducted by weighing all the reagents except the ligand in air, followed by addition of the ligand and degassed DMF by syringe occurred with rates and yields that were similar to those of reactions conducted with more rigorously dry conditions.

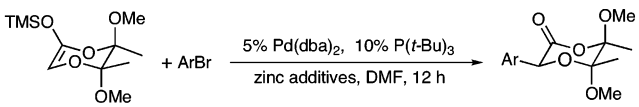
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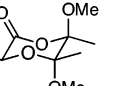
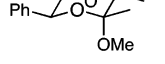
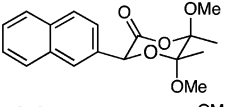
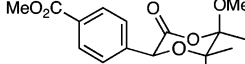
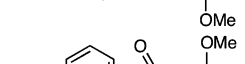
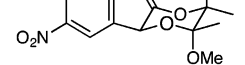
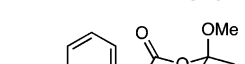
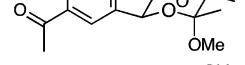
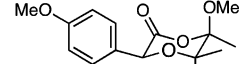
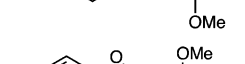
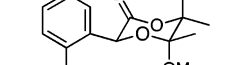
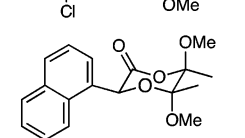
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Table 5. Arylation of the Silicon Enolate of Ley's Dioxanone


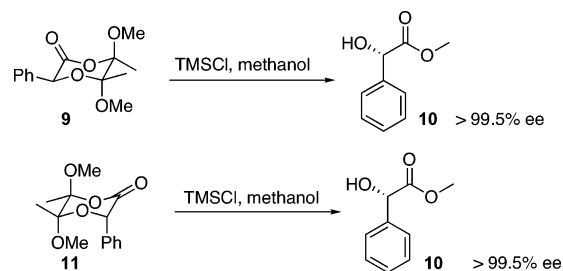
entry	product	zinc additive	T (°C)	yield ^a	d.r. ^b
1		0.5 eq ZnF ₂	80	67%	>50 : 1 ^c
2		0.25 eq Zn(Ot-Bu) ₂ ^d	rt	73%	>50 : 1
3		0.5 eq ZnF ₂	80	58%	>50 : 1
4		0.25 eq Zn(Ot-Bu) ₂ ^d	rt	80%	>50 : 1
5		0.5 eq Zn(Ot-Bu) ₂ ^d	rt	95%	>50 : 1
6		0.25 eq Zn(Ot-Bu) ₂ ^d	rt	78%	>50 : 1
7		0.5 eq Zn(Ot-Bu) ₂ ^d	rt	89%	>50 : 1
8		1.0 eq ZnF ₂	80	64%	>26 : 1
9		1.0 eq ZnF ₂	80	76%	25:1
10		0.5 eq ZnF ₂	80	57%	>50 : 1
11		1.0 eq ZnF ₂	80	78%	20:1
12		1.0 eq ZnF ₂	80	72%	>50:1

^a Isolated yields of reactions on 0.5 mmol to 1.0 mmol scale; average of two runs. ^b Ratios determined by integration of ¹H NMR spectra of crude reactions. ^c Diastereomeric ratio was stated to be ">50:1" when only one isomer was observed by NMR spectroscopy of the crude reaction mixture. ^d Commercial zinc *t*-butoxide contains roughly 50 wt % water, as determined by NMR spectroscopy. The number of equivalents of zinc alkoxide was calculated assuming the commercial zinc *t*-butoxide is 50 wt %.

The diastereomeric ratios of the arylated products were determined by ¹H NMR spectroscopy. The most stable diastereomer has been established to contain the alkyl or aryl substituents in the equatorial position and methoxy groups in the axial position.⁴⁴ The major isomer from the catalytic reaction was shown to be this thermodynamically more stable isomer. Spectral data on the minor isomeric product for comparison to that of the major product were obtained from samples of the two diastereomers generated by protonation of the lithium enolate of the arylated product at low temperature⁵³ with *t*-butanol and acetic acid.

To ensure this arylation of Ley's reagent would lead to an enantioselective synthesis of α -hydroxy esters, the enantiopure isomer was deprotected. As shown in Scheme 3, both diastereomers were individually treated with TMSCl in methanol,⁴⁴ and the optical purity of the resulting methyl mandelic ester was determined to be greater than 99.5%. Thus, deprotection of the arylated product preserves the stereochemistry created in the coupling step as expected.⁴⁴

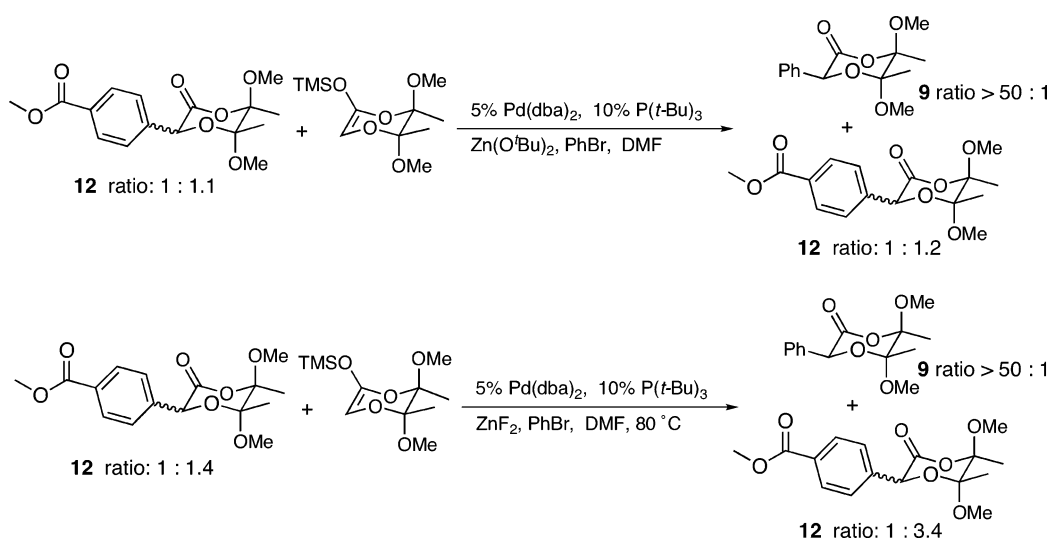
Two experiments were conducted to determine whether the observed diastereomeric ratio was controlled by kinetic or

Scheme 3

thermodynamic factors. First, we monitored by ¹H NMR spectroscopy the reaction of PhBr with the silyl enolate of the dioxanone **8** catalyzed by P(*t*-Bu)₃ and Pd(dba)₂ with zinc *t*-butoxide as an additive. If the ratio was determined by the relative thermodynamic stability of the two diastereomers, we might observe the accumulation of the minor isomer during the reaction, followed by epimerization of this material to the major isomer. Only the major isomer was observed during the reaction.

Second, we tested for epimerization of the components of a diastereomeric mixture of the arylated products. A 1:1.1 ratio

Scheme 4



of the two epimers of the α -aryl dioxanone **12** was added to the reaction of the enolate of **8** with phenyl bromide in the presence of $\text{Zn(O}^t\text{Bu)}_2$ as an additive and Pd(dba)_2 and $\text{P}(t\text{-Bu)}_3$ as catalysts, as shown in Scheme 4. The 1:1.1 mixture of diastereomers **12** did not change measurably during this reaction. A 1:1.4 mixture of diastereomers **12** changed to a 1:3.4 mixture that favored the major diastereomer of the catalytic reaction when the same process was conducted with ZnF_2 as an additive. These data suggest that some epimerization could occur with the less reactive system containing zinc fluoride, but this small amount of epimerization cannot account for the high diastereoselectivities observed from the coupling of the silyl enolate of **8** with aryl halides.

The diastereoselectivity of the catalytic arylation indicates that the arylpalladium halide approaches the silicon enolate from the same direction that an alkyl halide approaches the lithium enolate. The palladium would approach the enolate more favorably from the less hindered equatorial site to avoid the unfavorable 1,3-diaxial interaction with the methoxy groups. Our selectivity compares well with the 60:1 ratio of diastereomers reported by Ley and co-workers from reaction of allylic bromides with the lithium enolate of **8**,⁴⁴ despite the temperature of the catalytic arylation being much higher than that of the uncatalyzed alkylation.

Possible Role of Zinc Additives. The mechanism by which the zinc additives promote the coupling of the silicon enolates is ambiguous, but we have obtained several lines of data that argue against a complete transmetalation of silicon to zinc. One might propose that reaction of the silicon enolates with ZnF_2 would generate a zinc enolate because the F–Si bond is strong and fluoride is commonly used to cleave silicon–oxygen bonds. Moreover, we have recently shown that Reformatsky reagents react with aryl halides to form α -aryl esters and amides.^{25,26} However, the scope of the reactions with the silicon enolate and zinc halide is different from that of the Reformatsky reagents. For example, 4-bromoacetophenone reacts in high yield with the silyl enolate of *tert*-butyl propionate and zinc additive, but this substrate suffers attack at the carbonyl group by the Reformatsky reagents.

Moreover, no direct evidence for transmetalation was observed upon reaction of the silicon enolates with zinc halides.

Reaction of the trimethylsilylenolate of methyl isobutyrate with ZnF_2 in DMF at 80°C for 12 h led to decomposition of about 50% of the silyl ketene acetal to the ester without accumulation of a new enolate, whereas the catalytic reaction occurred to completion within this time. In addition, monitoring of the reaction of Ley's reagent with phenyl bromide in the presence of the palladium catalyst and $\text{Zn(O}^t\text{Bu)}_2$ as an additive showed no evidence for the accumulation of a zinc enolate. Only the decay of the silicon enolate and the accumulation of coupled product and a small amount of ester from hydrolysis was observed. Therefore, if a zinc enolate were generated as an intermediate during this process, its formation must be endergonic, and the resulting enolate must react quickly with the palladium.

Furthermore, the use of only 0.25 equiv of ZnF_2 provided the coupled product from reaction of methyl trimethylsilyl ketene acetal with PhBr in 93% yield as determined by GC. Clearly, stoichiometric amounts of fluoride are not required for the reaction to occur to completion. In addition, zinc bromide or a mixed fluorozinc bromide would have to be an effective promoter if fluoride-catalyzed cleavage of the silicon enolate occurred because the transmetalation with an arylpalladium bromide complex would generate a zinc bromide. ZnBr_2 does serve as a mild promoter of the arylation of the silyl ketene acetals, but reaction of methyl trimethylsilyl ketene acetal with phenyl bromide in the presence of the palladium catalyst and ZnBr_2 gave only 38% yield of the coupled product after 12 h at 80°C . Use of an admixture of ZnBr_2 and ZnF_2 as a promoter also did not lead to full conversion of phenyl bromide under the same reaction conditions.

Thus, three possible roles of the zinc additive are consistent with our data. The zinc additive might function as a Lewis acid to reduce the strength of the silicon–oxygen bond, and the aprotic polar solvent DMF could function as a Lewis base to further activate the silyl enolate. Second, the zinc additive might abstract halide from palladium to generate a more positively charged palladium center that would undergo faster transmetalation. Third, the silylketene acetal could be transformed into a zinc enolate in a thermodynamically unfavorable but kinetically accessible step. The resulting enolate could then react rapidly

with palladium, and the fluoride from silicon could be returned to the resulting zinc bromide to regenerate the zinc fluoride.

Conclusions

The arylation of the preformed silicon enolates in the presence of zinc additives in DMF provides a process that is complementary to previously published arylation of alkali metal enolates and Reformatsky reagents. This procedure tolerates various functional groups, such as nitro, cyano, ester, and ketone substituents, on the aryl bromide. Furthermore, the thermal stability of the silicon enolates makes them suitable for the first formation of α -aryl- α -alkoxy esters by coupling of the corresponding enolates with aryl halides. On the other hand, these reactions are slower than those of the alkali metal enolates and Reformatsky reagents and require polar solvents. Thus, each method displays advantages, and the combination of methods provides a catalytic route to a variety of α -aryl ester derivatives.

The development of conditions for the arylation of silicon ester enolates has allowed the preparation of products with stereogenic centers α to the carbonyl group. We have developed two processes with substrates bearing established chiral auxiliaries, and the diastereomeric ratios have been shown to reflect kinetic selectivities. Significant diastereoselectivities have been observed for the arylation of imides bearing the Evans auxiliary. These reactions provide an enantioselective synthesis of tertiary α -aryl acids. In addition, excellent diastereoselectivities were achieved from the arylation of Ley's auxiliary, and this reaction provides an enantioselective synthesis of α -arylated α -hydroxy esters. Successful diastereoselective arylation with these auxiliaries suggests that this methodology may be conducted with silicon enolates of other carbonyl derivatives bearing chiral auxiliaries and can be applied to the synthesis of structurally complex products, even at the latter stages of a synthesis. A related reaction was employed previously in the synthesis of a leukotriene B₄ antagonist.³⁰ Use of the catalyst and additive of the current work would increase the efficiency of the coupling step of this synthesis and would simplify the experimental procedures.

Experimental Section

General Methods. Reactions were conducted using standard drybox techniques. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a 400 MHz spectrometer with tetramethylsilane or residual protiated solvent used as a reference and coupling constants reported in hertz (Hz). Chromatographic purifications were performed by flash chromatography using silica gel (200–400 mesh) or using an automated chromatography system. Yields for final products in all tables refer to isolated yields and are the average of two runs. Products that had been reported previously were isolated in greater than 95% purity, as determined by ¹H NMR and capillary gas chromatography (GC). All ¹³C NMR spectra were proton decoupled. GC analyses were obtained with a DB-1301 narrow bore column for high-temperature ramp applications (max 120 °C/min). Methyl trimethylsilyl ketene acetal, ZnF₂, and Zn(O^{*t*}Bu)₂ were purchased from commercial suppliers. The silyl ketene acetal of *tert*-butyl propionate⁵⁵ and the trimethylsilyl ether derivative of the Evans auxiliary⁵⁶ were prepared according to literature procedures. The racemic version⁵⁷ of the available nonracemic Ley

auxiliary⁴⁴ was used to determine diastereoselectivities and was prepared by literature procedures.

Representative Procedure for the Arylation of Silyl Ketene Acetals. Methyl phenylisobutyrate (Table 2, entry 1).¹⁵ To a screw-capped vial containing P^{*t*}Bu₃ (40 μ L of a 0.500 M solution in toluene, 0.020 mmol), Pd(dba)₂ (5.8 mg, 0.010 mmol), ZnF₂ (52.0 mg, 0.500 mmol), and phenyl bromide (157.0 mg, 1.000 mmol) was added *tert*-butyl trimethylsilyl methyl ketene acetal (301.0 mg, 1.49 mmol), followed by DMF (4.0 mL). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The heterogeneous reaction mixture was stirred at 80 °C for 12 h. The crude reaction was then allowed to cool to room temperature and diluted with Et₂O (50 mL). The resulting solution was washed with H₂O (5 \times 20 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated at reduced pressure. The residue was then purified by chromatography on silica gel, eluting with a 1–2% gradient of EtOAc in hexane to provide the title compound (162 mg) in 91% yield. ¹H NMR (CDCl₃): δ 7.27–7.38 (5H, m), 3.69 (3H, s), 1.62 (6H, s). ¹³C NMR (CDCl₃): δ 177.72, 145.08, 128.85, 127.15, 126.02, 52.64, 46.94, 26.98.

Arylation of Trimethylsilyl Ketenimines of the Evans Auxiliary. (4*S*,2'*S*)-4-Isopropyl-3-(2'-phenyl-propanoyl)oxazolidin-2-one (Table 3, Entries 1, 2).⁵⁸ To a screw-capped vial containing P^{*t*}Bu₃ (0.500 M solution in toluene, 200 μ L, 0.010 mmol), Pd(dba)₂ (29 mg, 0.050 mmol), ZnF₂ (52 mg, 0.50 mmol), and phenyl bromide (157 mg, 1.00 mmol) were added the trimethylsilyl enolate **2** of the Evans imide (370.0 mg, 1.44 mmol), followed by DMF (10 mL). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The heterogeneous reaction mixture was stirred at 80 °C for 12 h. The crude reaction was then allowed to cool to room temperature and diluted with Et₂O. The resulting solution was washed with H₂O. The organic phase was dried over Na₂SO₄, filtered, and concentrated at reduced pressure. Purification of the crude material by flash chromatography, eluting with 2% EtOAc in hexanes, gave 67% yield of the α -aryl imide. ¹H NMR (CDCl₃): δ 7.27 (2H, d, *J* = 7.4 Hz), 7.22 (2H, t, *J* = 7.3 Hz), 7.15 (1H, t, *J* = 7.3 Hz), 5.06 (1H, q, *J* = 7.0 Hz), 4.25–4.28 (1H, m), 4.00–4.07 (2H, m), 2.33–2.37 (1H, m), 1.43 (3H, d, *J* = 7.0 Hz), 0.84 (3H, d, *J* = 6.6 Hz), 0.82 (3H, d, *J* = 6.1 Hz). ¹³C NMR (CDCl₃): δ 175.04, 153.99, 140.72, 128.98, 128.56, 127.59, 63.50, 59.43, 43.45, 28.94, 20.09, 18.42, 15.11.

Experimental Procedure for the Evaluation of Epimerization during the α -Arylation. To a screw-capped vial containing P^{*t*}Bu₃ (0.500 M solution in toluene, 20 μ L, 0.010 mmol), Pd(dba)₂ (2.9 mg, 0.0050 mmol), ZnF₂ (5.2 mg, 0.050 mmol), and phenyl bromide (15.7 mg, 0.100 mmol) were added the trimethylsilyl enolate **2** of the Evans imide (37.0 mg, 0.144 mmol) and compound **1** (>90% de),⁵⁸ followed by DMF (1.0 mL). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The heterogeneous reaction mixture was stirred at 80 °C for 12 h. The crude reaction was then allowed to cool to room temperature and diluted with Et₂O (5.0 mL). The resulting solution was washed with H₂O (5 \times 2.0 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated at reduced pressure. The residue was then analyzed by ¹H NMR spectroscopy. Only one set of signals was observed for compound **1** and its (2')epimer.⁵⁸ From integration of the ¹H NMR signals, the diastereomeric ratio of the isopropyl derivative formed from the α -arylation was 88:12. The same reaction on a 1.00 mmol scale in the absence of the added α -aryl imide provided the major diastereomer in 67% yield after purification by flash chromatography eluting with 2% EtOAc in hexanes.

Representative Procedures for the Arylation of the Ley Auxiliary. 5,6-Dimethoxy-5,6-dimethyl-3-phenyl-[1,4]dioxan-2-one (Table 5, Entries 1, 2).⁵⁷ 5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one **8**^{44,57} (1.00 g, 5.26 mmol) was dissolved in anhydrous THF (20 mL), and

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the mixture was cooled to $-78\text{ }^{\circ}\text{C}$ under N_2 . LDA (3.2 mL of a 2.0 M solution in THF/heptane, 6.4 mmol) was then added dropwise. After addition, the mixture was stirred for another 5 min before addition of TMSCl (0.83 mL, 6.6 mmol). The resulting solution was then allowed to warm to room-temperature overnight. The THF was then removed under reduced pressure, and hexanes (20 mL) were added to the residue. The resulting suspension was filtered through Celite, and the hexanes were removed in vacuo to afford 1.40 g of the desired trimethylsilyl ketene acetal (judged to be 90–95% pure from NMR). ^1H NMR (CDCl_3): δ 5.55 (1H, s), 3.41 (3H, s), 3.26 (3H, s), 1.49 (3H, s), 1.42 (3H, s), 0.25 (9H, s). This material was directly employed in the arylation step. In a drybox, to a screw-capped vial were added PhBr (78.5 mg, 0.500 mmol), ZnF_2 (26.0 mg, 0.0250 mmol), $\text{Pd}(\text{dba})_2$ (15.0 mg, 0.025 mmol), and $\text{P}(\text{tBu})_3$ (100 μL , 0.50 M solution in toluene, 0.050 mmol). The trimethylsilyl ketene acetal prepared above (170 mg calculated according to the purity, 0.650 mmol) was added to the mixture followed by 4.0 mL of DMF. The vial was then sealed and heated at $80\text{ }^{\circ}\text{C}$ for 12 h. The solution was then allowed to cool to room temperature and partitioned between ethyl ether (50 mL) and water (10 mL). The ether layer was washed with water and brine and dried over Na_2SO_4 . After the ether was removed, the residue was subjected to automated flash chromatography using 8% EtOAc/hexanes to provide the desired product (88.4 mg) in 66% yield. ^1H NMR (CDCl_3): δ 7.59 (2H, d, $J = 6.8\text{ Hz}$), 7.32–7.41 (3H, m), 5.21 (1H, s), 3.47 (3H, s), 3.45 (3H, s), 1.58 (3H, s), 1.52 (3H, s). ^{13}C NMR (CDCl_3): δ 168.85, 136.44, 129.01, 128.91, 128.22, 105.65, 98.98, 74.07, 50.46, 49.78, 18.40, 17.47.

Procedure for Conducting the Reactions without a Glovebox.

To a round-bottom flask were added $\text{Pd}(\text{dba})_2$ (2.9 mg, 0.0050 mmol), $\text{Zn}(\text{O}^i\text{Bu})_2$ (21.0 mg of commercial material, which is about 50% H_2O by weight), the trimethylsilyl enolate of the Ley auxiliary (34.0 mg of calculated according to the purity, 0.130 mmol) and 3-bromonitrobenzene (20.2 mg, 0.100 mmol). The flask was purged with N_2 for 5 min before addition of $\text{P}(\text{tBu})_3$ (20 μL of 0.5 M solution in toluene, 0.010 mmol). DMF (1.0 mL) was then added, and the resulting mixture was stirred for 12 h. Trimethoxybenzene as an internal standard was then added to the solution, and the mixture was partitioned between Et_2O (5.0 mL) and H_2O (2.0 mL). The ether layer was washed with water, and the ether was evaporated in vacuo. The yield determined by NMR spectroscopy was determined with an internal standard to be nearly quantitative, which is similar to the yield observed when the reactions are assembled in a drybox.

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

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