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Palladium-Catalyzed Intermolecular α-Arylation of Zinc Amide Enolates under Mild Conditions

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Abstract: The intermolecular α-arylation and vinylation of amides by palladium-catalyzed coupling of aryl bromides and vinyl bromides with zinc enolates of amides is reported. Reactions of three different types of zinc enolates have been developed. The reactions of aryl halides occur in high yields with isolated Reformatsky reagents generated from α-bromo amides, with Reformatsky reagents generated in situ from α-bromo amides, and with zinc enolates generated by quenching lithium enolates of amides with zinc chloride. This use of zinc enolates, instead of alkali metal enolates, greatly expands the scope of amide arylation. The reactions occur at room temperature or 70 °C with bromoarenes containing cyano, nitro, ester, keto, fluoro, hydroxyl, or amino functionality and with bromopyridines. Moreover, the reaction has been developed with morpholine amides, the products of which are precursors to ketones and aldehydes. The arylation of zinc enolates of amides was conducted with catalysts bearing the hindered pentaphenylferrocenyl di-*tert*-butylphosphine (Q-phos) or the highly reactive, dimeric, Pd(I) complex $\{[P(t\text{-}Bu)_3]PdBr\}_2$.

Introduction

The α-aryl carbonyl unit is found in many pharmaceuticals and compounds with other biological activities.[1−6] Perhaps most important, α-aryl carbonyl compounds are precursors to compounds with alcohol, amine, olefin, imine, nitrile, and other functional groups located α or β to an aryl ring.

Although the uncatalyzed formation of the C−C bond between an aryl electrophile and an enolate is a useful transformation, methods for this type of C−C bond formation are limited in scope, are often incompatible with auxiliary functionality, or employ toxic reagents. Such carbon−carbon bonds have been formed by photochemical reactions,[7,8] reactions via benzyne intermediates,[9−11] and reactions with organobismuth[12−14] or aryllead reagents.[12,15−22] Reaction of an aryl Grignard reagent with the salt of an α-bromopropionic acid has also been used to generate α-aryl propionic acids.[23] Thus, many now traditional approaches have been developed to prepare α-aryl carbonyl compounds, but none of the methods has emerged as a general one.

The palladium-catalyzed α-arylation of carbonyl compounds has been introduced as a mild catalytic method to form the C−C bond between an aryl ring and the α-position of a carbonyl compound.[24,25] A variety of reactions of ketone[24,26−50] and ester[24,51−56] enolates have now been reported, but the α-arylation

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of amides, with one exception,[57] has been limited to reactions of lactams or intramolecular reactions of acyclic amides.[24,57−63] The α-arylation of amides requires a stronger base to generate the enolate than the α-arylation of ketones and esters, and the use of this strong base has several significant drawbacks. For example, the need for a strong base limits the scope of coupling reactions to electron-neutral or electron-rich aryl halides and aryl halides that lack protic or electrophilic functionality. In addition, the strongly basic conditions lead to catalyst decomposition, and the coupling of amides has required higher loadings of palladium than the coupling of ketone or ester enolates. Further, the α-aryl amide product quenches the starting enolate, and products from diarylation have been formed. Finally, the strongly basic conditions prevent asymmetric α-arylations that would form tertiary stereocenters.

To overcome these problems, a reaction that occurs with enolates that are less basic than alkali metal enolates of amides must be developed. Although zinc enolates of amides are not common reagents, they can be formed from the α-bromo amide[64] or by quenching of an alkali metal amide enolate with zinc halide.[65,66] Considering the greater functional group tolerance of the coupling of aryl and alkyl zinc reagents[67−69] than that of the coupling of aryl and alkyl magnesium or lithium reagents,[70,71] we anticipated that the coupling of zinc enolates of amides could address the problem of functional group tolerance of the coupling of amide enolates.

Little structural data is available on zinc enolates of amides, but the structures of zinc enolates of esters have been revealed by several methods. As determined by X-ray diffraction of the bromozinc enolate of *tert*-butyl and ethyl acetate bound by two tetrahydrofuran (THF) molecules, the enolates are dimeric in the solid state, and the zinc is bound to the oxygen of one enolate and the carbon of another.[72,73] Although the structures of the zinc enolates of propionates and isobutyrates are not known from X-ray diffraction, NMR data suggests that the zinc ion of these zinc enolates is also bound to carbon.[74,75]

A few limited examples of palladium-catalyzed α-arylations of zinc enolates have been reported. We first reported in communication form several examples of the coupling of aryl bromides with zinc enolates of amides formed from the corresponding α-halo amides.[76] These reactions were conducted with isolated zinc amides, which can be cumbersome to manipulate, and the reported reactions were limited to those of *N*,*N*-diethylacetamide and *N*,*N*-diethylpropionamide. Recently, Cossy and co-workers reported the palladium-catalyzed coupling of aryl bromides with zinc enolates of δ-lactams generated in situ.[63,77−79] The scope of these reported reactions was limited to this class of cyclic amide and to aryl halides that lacked potentially reactive protic or electrophilic functional groups, such as cyano, nitro, ester, keto, hydroxyl, and amino groups.

Here, we present a full account of the scope and limitations of a mild, more general palladium-catalyzed coupling of zinc enolates of amides that are generated in situ from α-bromo amides or from quenching of the alkali metal amide. The scope of these reactions now encompasses the coupling of acyclic acetamides, propionamides, isobutyramides, and morpholine amides with aryl halides that are electron-rich or electron-poor and that contain typically reactive, protic and electrophilic functional groups.

Results and Discussion

1. Arylation of Reformatsky Reagents of Amides. A. α-Arylation of Isolated Refomatsky Reagents. Our initial studies of palladium-catalyzed α-arylation of zinc enolates of amides were performed using isolated Reformatsky reagents.[76] Although this reaction requires the conversion of an amide to an α-bromo amide or the synthesis of the α-bromo amide from the appropriate acid bromide, the use of isolated Reformatsky reagents allowed us to eliminate the effects that could arise from formation of the enolate in situ.

The catalyst and temperatures needed for reactions of Reformatsky reagents of amides were much different from those needed for the α-arylation of alkali metal amide enolates.[24] Unlike the reactions of alkali metal amide enolates, the α-arylation of zinc enolates occurred in low yields with palladium catalysts ligated by 1,1′-binaphthalene-2,2′-diylbis-(diphenylphosphine) (BINAP) or carbene ligands. Instead, the reaction occurred in the presence of the palladium catalyst generated from $Pd(dba)_2$ (dba = 1,5-diphenyl-1,4-pentadien-3-one) and 1,2,3,4,5-pentaphenyl-1′-di-*tert*-butylphosphinoferrocene (Q-phos)[80−82] or in the presence of the dinuclear

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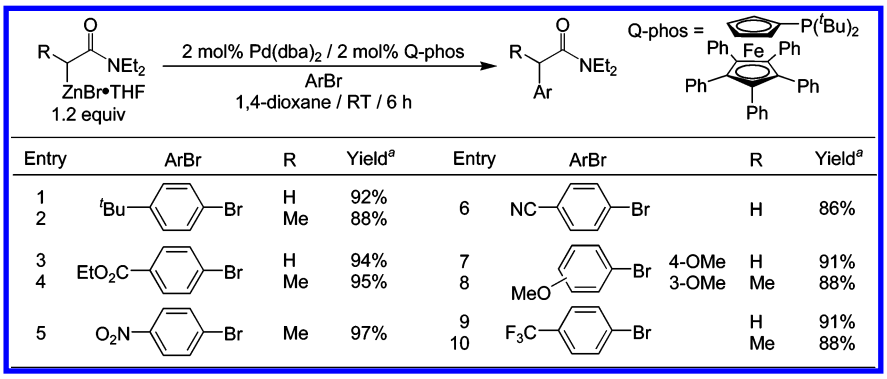
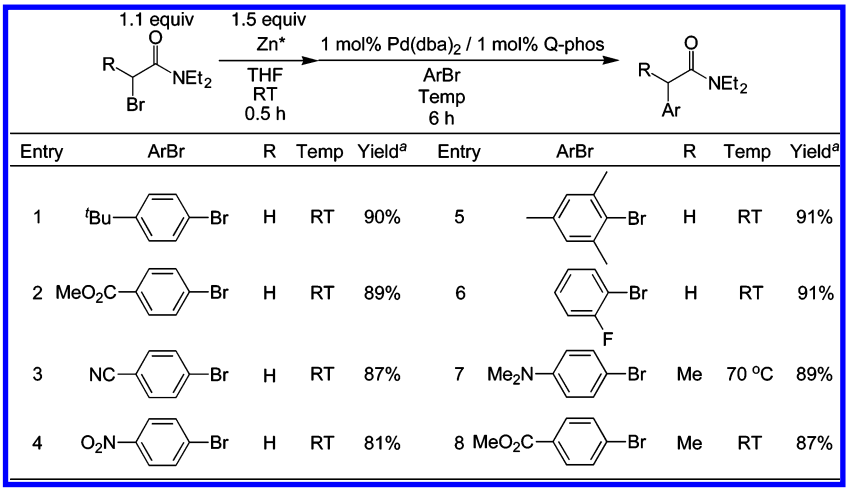
Table 1. Arylation of Isolated Reformatsky Reagents



Entry	ArBr	R	Yield[a]	Entry	ArBr		R	Yield[a]
1	4-tBu	H	92%	6	4-NC		H	86%
2	4-tBu	Me	88%					
3	4-EtO2C	H	94%	7	4-MeO	4-OMe	H	91%
4	4-EtO2C	Me	95%	8	4-MeO	3-OMe	Me	88%
5	4-O2N	Me	97%	9	4-F3C		H	91%
				10	4-F3C		Me	88%

[a] Isolated yields (average of two runs) for reactions of 1 mmol of bromoarene in 18 mL of dioxane.

Table 2. Arylation of Diethylacetamide and Diethylpropionamide Reformatsky Reagents Generated in Situ from the α-Bromo Amide and Activated Zinc



Entry	ArBr	R	Temp	Yield[a]	Entry	ArBr	R	Temp	Yield[a]
1	4-tBu	H	RT	90%	5	4-Ph	H	RT	91%
2	4-MeO2C	H	RT	89%	6	4-F	H	RT	91%
3	4-NC	H	RT	87%	7	4-Me2N	Me	70 °C	89%
4	4-O2N	H	RT	81%	8	4-MeO2C	Me	RT	87%

[a] Isolated yields (average of two runs) for reactions of 0.5 mmol of bromoarene in 2 mL of THF.

Pd(I) complex, $\{[P(t\text{-}Bu)_3]PdBr\}_2$.[83−85] In contrast to the elevated temperatures required for the coupling of alkali metal amides catalyzed by palladium complexes of BINAP, the α-arylation of isolated Reformatsky reagents of amides occurred at room temperature in the presence of the palladium catalyst ligated by Q-phos or the dinuclear Pd(I) catalyst. As will be shown by the examples described in the next paragraph, the lower temperatures of these reactions of zinc enolates help prevent side reactions, such as the addition of zinc enolates to electrophiles. In addition, the reactions of less basic Reformatsky reagents led to selective formation of monoarylation products instead of the mixture of monoarylation and diarylation products obtained from the reactions of alkali metal amides.

Table 1 summarizes several reactions of aryl bromides with isolated Reformatsky reagents of amides. These reactions demonstrate the potential of zinc enolates of amides to create a general route to α-aryl amides. Reactions of diethylacetamide and diethylpropionamide occurred in comparable yields with the bromoarenes tested. The reactions occurred with electron-neutral (entries 1 and 2), electron-rich (entry 7), and electron-poor (entries 8−10) bromoarenes with substituents that would be expected to be stable to an enolate nucleophile. However, the reaction also occurred in high yield with bromoarenes containing ester, nitro, and cyano groups. These data suggested that a procedure to conduct the same types of couplings with amide enolates of zinc generated in situ from the α-bromo amide or from the alkali metal enolate would create a convenient and general process to form α-aryl amides.

B. α-Arylation of Reformatsky Reagents Generated in Situ. After having developed conditions to conduct the coupling of isolated Reformatsky reagents with aryl bromides, we were interested in developing a more practical procedure that would occur with Reformatsky reagents generated in situ. Because we were able to develop conditions to couple aryl halides with zinc enolates of acetamides and propionamides generated from the alkali metal enolates (vide infra), we focused on the coupling of aryl halides with the Reformatsky reagents of isobutyramides. However, to draw comparisons between the chemistry of the isolated Reformatsky reagents and those generated in situ, we also conducted reactions with diethylacetamide and diethylpropionamide enolates generated in situ from the α-bromo amide and activated zinc metal.

Table 2 summarizes results from reactions of the Reformatsky reagents of diethylacetamide and diethylpropionamide with bromoarenes. These bromoarenes contain substituents that are electron-donating or electron-withdrawing, some of which are incompatible with an alkali metal enolate. The enolate was generated first by reaction of activated zinc metal[86] with the

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α-bromo amide at room temperature in THF. To the resulting enolate were then added the bromoarene and catalyst. By this procedure, reactions of electron-neutral and electron-poor bromoarenes occurred at room temperature in high yield. These reactions were compatible with ester, nitrile, and nitro functionality. They occurred with the 2,6-disubstituted bromomesitylene and with the strongly electron-donating *p*-dimethylamino group on the arene ring.

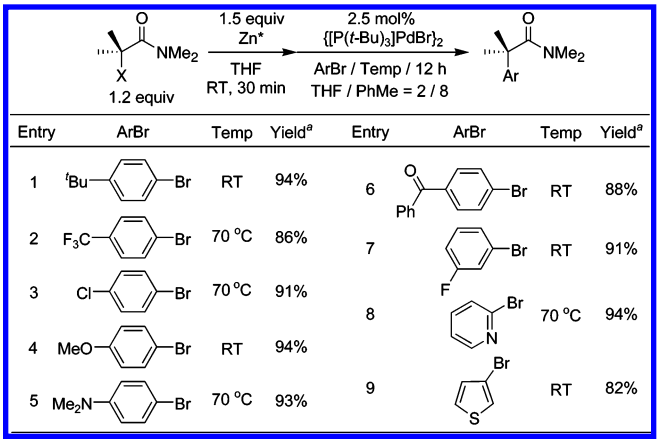
C. α-Arylation of Zinc Enolates Prepared from α-Bromoisobutyramides. Because alkali metal enolates of α,α-disubstituted amides are difficult to generate, the coupling of Reformatsky reagents of α-bromoisobutyramides is a particularly valuable transformation. The conditions for the development of reactions of isobutyramides were derived from initial studies of the reactions of morpholine α-bromoisobutyramide described in section 3.C. These experiments to develop reaction conditions for isobutyramide enolates are summarized in Table S1 of the Supporting Information.

In contrast to the coupling of *N*,*N*-dimethylisobutyramide with bromoarenes in the presence of lithium diisopropylamide (LDA), lithium dicyclohexylamide ($LiNCy_2$), and *sec*-butyllithium, which occurred in low yields with all catalysts we have tested, many couplings of aryl bromides and heteroaryl bromides with the Reformatsky reagent of *N*,*N*-dimethylisobutyramide occurred in moderate to good yields. The couplings of the isobutyramide enolates occurred in low yield with the palladium catalyst generated from $Pd(dba)_2$ and Q-phos. However, the same reactions catalyzed by the dimeric Pd(I) complex, $\{[P(t\text{-}Bu)_3]PdBr\}_2$, occurred in high yield. This difference in reactivity may result from the slightly more open structure of the arylpalladium halide complex with $P(t\text{-}Bu)_3$ as ligand.[87] The formation of the zinc enolate from the α-bromo isobutyramides required THF solvent, but side products from the reduction of aryl halides and homocoupling were the major products from the catalytic couplings of the morpholine isobutyramide enolate in THF. This limitation was overcome by forming the Reformatsky reagent in THF and conducting the catalytic reactions in a mixture of 80% toluene and 20% THF. This procedure with two solvents led to formation of the coupled product from reactions of the Reformatsky reagents of the isobutyramides in high yield.

Table 3 summarizes the scope of the coupling of the Reformatsky reagent of *N*,*N*-dimethylisobutyramide with bromoarenes catalyzed by the Pd(I) dimer. These examples show that the reaction occurs in high yield with a variety of electronically diverse bromoarenes. These results contrast with the low yields obtained from reactions of the alkali metal amide with aryl bromides and demonstrate the benefits of conducting cross-couplings with zinc enolates of amides. The results in Table 3 also demonstrate that the reaction occurs in the presence of a phenacyl group and with an aryl fluoride, which could activate the arene to deprotonation by the basic enolate and lead to formation of products from a benzyne intermediate. Finally, entries 8 and 9 of Table 3 show that the coupling also occurs with a bromopyridine and a bromothiophene.

At the same time, this highly basic enolate was incompatible with bromoarenes containing ester, nitro, or cyano functionality, which were tolerated by the reactions of the Reformatsky reagents of diethylacetamide and diethylpropionamide. Moreover, this hindered enolate did not couple with ortho-substituted bromoarenes.

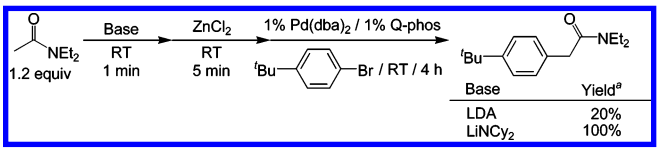
Table 3. Arylation of Dimethylisobutyramide Reformatsky Reagent Generated in Situ from the α-Bromo Amide and Activated Zinc



Entry	ArBr	Temp	Yield[a]	Entry	ArBr	Temp	Yield[a]
1		RT	94%	6		RT	88%
2		70 °C	86%	7		RT	91%
3		70 °C	91%	8		70 °C	94%
4		RT	94%				
5		70 °C	93%	9		RT	82%

[a] Isolated yields (average of two runs) for reactions of 0.5 mmol of bromoarene in a mixture of 1.2 mL of THF and 4.8 mL of toluene as solvent.

Scheme 1



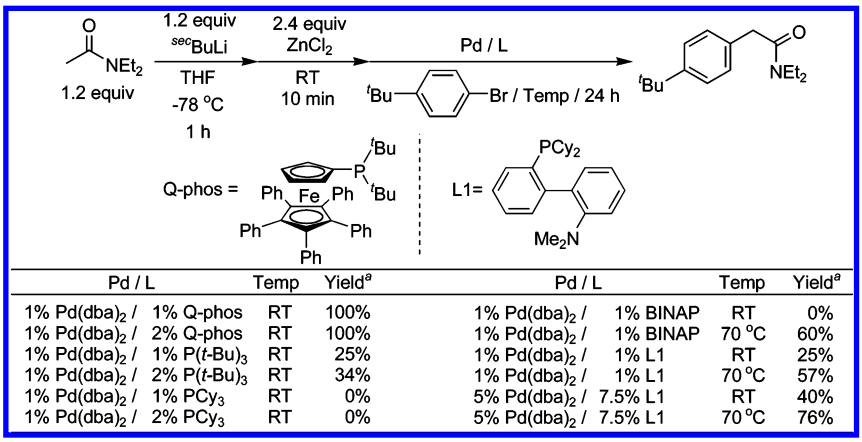
[a] Yields were determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard for reactions conducted with 0.25 mmol of bromoarene in 2.5 mL of THF; 2 equiv of LDA and 2 equiv of zinc chloride, or 1.2 equiv of lithium dicyclohexylamide and 1.2 equiv of zinc chloride were used.

2. α-Arylation of the Zinc Enolates of Acetamides, Propionamides, and Pentanamides Generated by Quenching Lithium Enolates with Zinc Chloride. A procedure to couple a zinc amide enolate that is generated directly from the amide, rather than from the α-bromoamide, would combine the functional group tolerance of the Reformatsky reagents and the convenience of the reactions of alkali metal enolates of amides. In addition, a procedure that forms the zinc enolate from a zinc halide would be simpler to conduct than a procedure that forms the zinc enolate using activated zinc metal. Thus, we sought conditions to conduct the α-arylation of enolates by quenching an alkali metal enolate of an amide with zinc chloride. The reactivity of enolates generated by quenching of alkali metal enolates with zinc halide and the reactivity of Reformatsky reagents generated from α-bromo amides are different. Yet, the use of certain bases to generate the alkali metal enolate precursor to the zinc enolate led to the development of a general coupling of acetamides, propionamides, and morpholine amides with haloarenes.

A. Development of Conditions for the α-Arylation of Acetamides with Zinc Enolates Formed from Alkali Metal Enolates. To develop the coupling of zinc amide enolates from alkali metal enolates, we surveyed reactions of enolates generated with different bases and zinc halides. As shown in Scheme 1, procedures in which the zinc enolate was generated from the lithium enolate by addition of zinc chloride formed the coupled products in yields that depended on the base. Considering the high pK_a of the amide enolate, we tested conditions in which

(86) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.
(87) Stambuli, J. P.; Buhl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346.

Table 4. Effect of Ligand Structure on the Arylation of Zinc Amide Enolates Generated via Lithium Amide Enolates



Pd / L	Temp	Yield[a]	Pd / L	Temp	Yield[a]
1% $Pd(dba)_2$ / 1% Q-phos	RT	100%	1% $Pd(dba)_2$ / 1% BINAP	RT	0%
1% $Pd(dba)_2$ / 2% Q-phos	RT	100%	1% $Pd(dba)_2$ / 1% BINAP	70 °C	60%
1% $Pd(dba)_2$ / 1% P(*t*-Bu)$_3$	RT	25%	1% $Pd(dba)_2$ / 1% L1	RT	25%
1% $Pd(dba)_2$ / 2% P(*t*-Bu)$_3$	RT	34%	1% $Pd(dba)_2$ / 1% L1	70 °C	57%
1% $Pd(dba)_2$ / 1% PCy_3	RT	0%	5% $Pd(dba)_2$ / 7.5% L1	RT	40%
1% $Pd(dba)_2$ / 2% PCy_3	RT	0%	5% $Pd(dba)_2$ / 7.5% L1	70 °C	76%

[a] Yields were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard for reactions conducted with 0.25 mmol of bromoarene in 2.5 mL of THF.

the enolate was generated from LDA or $LiNCy_2$, followed by quenching with zinc chloride. The reaction of 4-bromo-*tert*-butylbenzene with the enolate generated from diethylacetamide and LDA followed by quenching with $ZnCl_2$ formed the coupled product in low yield. In contrast, the reaction of 4-bromo-*tert*-butylbenzene with the enolate prepared from diethylacetamide and $LiNCy_2$ followed by quenching with $ZnCl_2$ formed the coupled product in high yields. However, reactions of aryl halides containing electron-deficient functional groups, such as ester, cyano, nitro, and trifluoromethyl groups, with this zinc enolate occurred in lower yields (0−42%).

Ultimately, we tested reactions of enolates generated from organolithium reagents. Cossy reported couplings of zinc enolates of δ-lactams generated from *sec*-BuLi,[63,78,79] and we tested this base for reactions of acetamides. The amount of zinc chloride used to quench the alkali metal enolates appeared to affect significantly the yields of coupled products. When 1 equiv of zinc chloride per enolate was used, only about 50% conversion to coupled product was observed, even after long reaction times. However, reactions of the enolate generated by quenching the alkali metal amide with 2.4 equiv of zinc chloride occurred to full conversion and formed the coupled product in high yield.

Of the catalysts we tested, the one generated from $Pd(dba)_2$ and Q-phos formed the coupled product in the highest yield with the lowest loadings of palladium (Table 4). Reactions with catalysts generated from $Pd(dba)_2$ and tri-*tert*-butylphosphine or tricyclohexylphosphine formed the coupled product in low yield. Cossy conducted the α-arylation of δ-lactams with a catalyst generated from one of the biphenyldialkylphosphines developed by Buchwald. Reactions of acetamides catalyzed by complexes generated from $Pd(dba)_2$ and this ligand formed the coupled product in lower yields than reactions catalyzed by complexes generated from $Pd(dba)_2$ and Q-phos, even at higher catalyst loadings.

B. Scope of the Couplings of Zinc Enolates of *N*,*N*-Dialkylacetamides Generated via Lithium Enolates. The scope of the α-arylation of the zinc enolates of acetamides generated from the alkali metal amide is summarized in Table 5. The protocol for these reactions is also shown at the top of Table 5. The zinc enolate was generated after reaction of the amide with *sec*-BuLi for 1 h at −78 °C, followed by quenching of the resulting lithium enolate with $ZnCl_2$. *N*,*N*-Dimethylacetamide and *N*,*N*-diethylacetamide underwent the α-arylation process with a wide range of bromoarenes at room temperature. As noted below, a few reactions required elevated temperatures, but these occurred only at 70 °C. In no case were products from diarylation of the enolate observed.

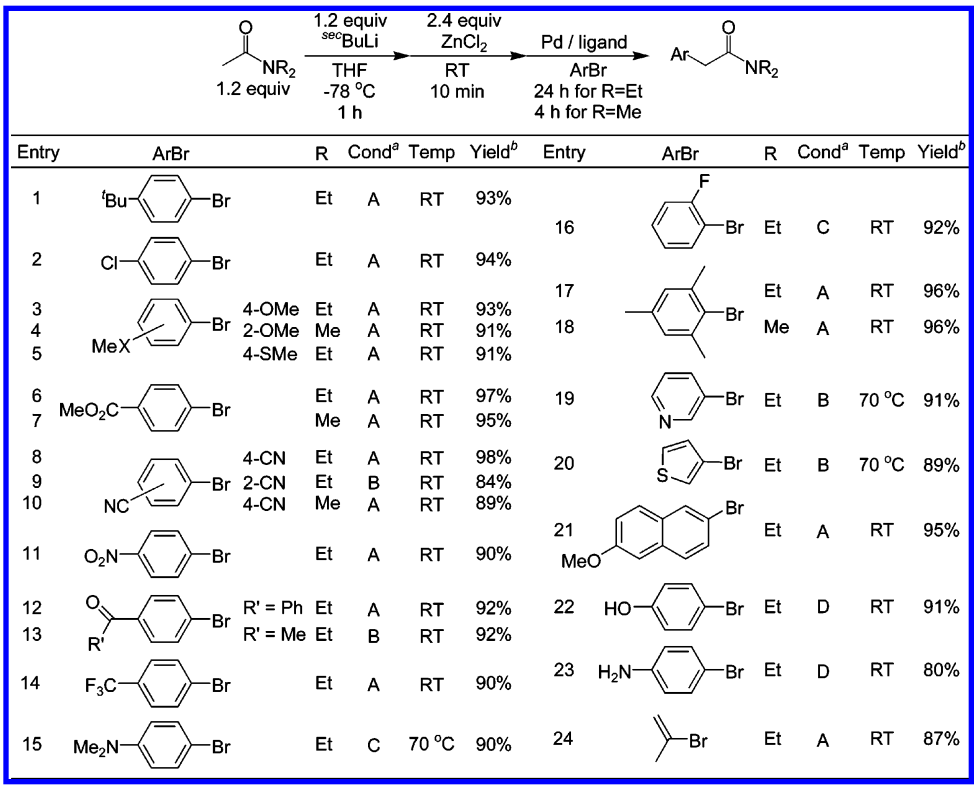
The arylation of *N*,*N*-diethylacetamide and *N*,*N*-dimethylacetamide encompassed reactions of electron-neutral, electron-rich, and electron-poor aryl bromides containing relatively unreactive substituents. Many of these reactions occurred in yields exceeding 90%. Moreover, the coupling process occurred with aryl bromides that contain functional groups that are not tolerant of strongly basic and nucleophilic amide enolates. For example, couplings of methyl 4-bromobenzoate, 2- and 4-bromobenzonitrile, 4-bromonitrobenzene, and 4-bromoacetophenone occurred in high yield. Moreover, coupling of the zinc enolate of *N*,*N*-diethylacetamide occurred with 3-bromopyridine and 3-bromothiophene in high yield at 70 °C, even though couplings of pyridyl or thienyl halides do not occur with most alkali metal enolates of ketones, esters, or amides.

The coupling of the zinc enolates of *N*,*N*-dialkylacetamides generated via the lithium enolates also occurred with bromoarenes containing free protic functionality. In addition to reaction with the enolizable 4-bromoacetophenone noted above, the zinc enolate reacted with 4-bromophenol and 4-bromoaniline to generate the desired α-aryl amide. Addition of 1.05 equiv of KH to deprotonate the hydroxyl or amino groups prior to addition of the enolate allowed these couplings to occur in high yield. These reactions occurred in high yield when the dimeric precatalyst $\{[P(t\text{-}Bu)_3]PdBr\}_2$ was used. The reaction was also selective for replacement of bromide over chloride and fluoride. Reaction of 4-chlorobromobenzene and 2-fluorobromobenzene led to formation of the product from replacement of bromide.

The reaction also occurred with aryl bromides containing one or two ortho substituents. The coupling process occurred with 2-bromobenzonitrile and with 2-fluorobromobenzene, which contain ortho substituents that can interfere with the palladium chemistry. Moreover, high yields of α-aryl amide were obtained with more sterically hindered bromoarenes, such as bromomesitylene.

In addition to reactions of bromoarenes, the coupling of acetamides occurred with vinyl bromides. While we have not

Table 5. Arylation of the Zinc Enolate of *N,N*-Diethylacetamide and *N,N*-Dimethylacetamide



Entry	ArBr	R	Cond[a]	Temp	Yield[b]	Entry	ArBr	R	Cond[a]	Temp	Yield[b]
1	4-*t*Bu	Et	A	RT	93%	16	2-F	Et	C	RT	92%
2	4-Cl	Et	A	RT	94%	17	3-Me	Et	A	RT	96%
3	4-OMe	Et	A	RT	93%	18	3-Me	Me	A	RT	96%
4	2-OMe	Me	A	RT	91%						
5	4-SMe	Et	A	RT	91%						
6	4-MeO_2C	Et	A	RT	97%	19	3-pyridyl	Et	B	70 °C	91%
7	4-MeO_2C	Me	A	RT	95%						
8	4-CN	Et	A	RT	98%	20	2-thienyl	Et	B	70 °C	89%
9	2-CN	Et	B	RT	84%						
10	4-CN	Me	A	RT	89%	21	6-MeO-2-naphthyl	Et	A	RT	95%
11	4-O_2N	Et	A	RT	90%	22	4-HO	Et	D	RT	91%
12	4-C(O)R', R' = Ph	Et	A	RT	92%	23	4-H_2N	Et	D	RT	80%
13	4-C(O)R', R' = Me	Et	B	RT	92%						
14	4-F_3C	Et	A	RT	90%	24	4-vinyl	Et	A	RT	87%
15	4-Me_2N	Et	C	70 °C	90%						

[a] Conditions: (A) 1 mol % $Pd(dba)_2$, 1 mol % Q-phos; (B) 2 mol % $Pd(dba)_2$, 2 mol % Q-phos; (C) 3 mol % $Pd(dba)_2$, 3 mol % Q-phos; (D) 0.5 mol % $\{[P(t\text{-}Bu)_3]PdBr\}_2$, 1.05 equiv of KH. [b] Isolated yields (average of two runs) for reactions of 0.5 mmol of bromoarene in 5 mL of THF.

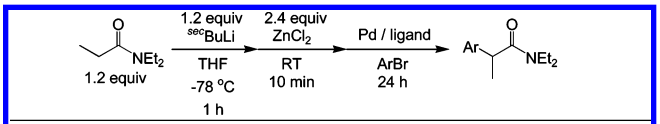
studied these reactions extensively, the coupling of *N,N*-diethylacetamide with the commercially available bromopropene occurred in high yield at room temperature.

In most cases, reactions of dimethylacetamide and diethylacetamide occurred similarly.[88] However, the reaction of 2-bromobenzonitrile with the zinc enolate of *N,N*-dimethylacetamide occurred to only about 30% conversion under the same conditions that the reaction of diethylacetamide occurred in high yield, and the reaction of 4-bromoacetophenone with the zinc enolate of *N,N*-dimethylacetamide occurred in somewhat lower yield than the reaction of *N,N*-diethylacetamide.

Although the scope of these couplings was broad, the coupling of acetamides does have some limitations. For example, reaction of the zinc amide of diethylacetamide with 2-bromopyridine did not occur, even though coupling with 3-bromopyridine occurred in high yield. Although the zinc counterion tempers the reactivity of the enolate, the zinc enolate does remain nucleophilic enough to react with strong electrophiles in competition with the coupling process. For example, zinc acetamide enolates reacted with 4-bromobenzaldehyde to form aldol products instead of products from cross-coupling at the halide. Similarly, the reaction of this zinc enolate with 4-bromobenzyl bromide formed products from nucleophilic substitution at the benzylic position.

C. Coupling of the Zinc Enolates of Propionamides Generated via the Alkali Metal Enolate. The couplings of the zinc enolate of *N,N*-diethylpropionamide generated by quenching of the lithium enolate with zinc chloride are summarized in Table 6. These reactions occurred in a fashion similar to those of the analogous zinc enolate of *N,N*-diethylacetamide. Like the reactions of *N,N*-diethylacetamide, the reactions of *N,N*-diethylpropionamide were conducted by deprotonation of the amide at −78 °C, followed by quenching with 2 equiv of zinc chloride per enolate at room temperature. Most

Table 6. Arylation of the Zinc Enolate of *N,N*-Diethylpropionamide



Entry	ArBr	Cond[a]	Temp	Yield[b]	Entry	ArBr	Cond[a]	Temp	Yield[b]
1	4-F_3C	A	RT	90%	9	4-MeO	A	RT	94%
2	4-Cl	A	RT	87%	10	4-MeS	A	RT	91%
3	3-Br	C	RT	98%	11	3-pyridyl	C	70 °C	86%
4	4-Br, 3-OMe	C	RT	88%	12	2-thienyl	A	70 °C	92%
5	3-Br, 4-F	C	RT	86%	13	4-HO	D	RT	95%
6	4-NC	C	RT	91%	14	4-H_2N	D	RT	90%
7	4-O_2N	C	RT	87%	15	4-vinyl	A	RT	92%
8	6-Br, 2-MeO	B	RT	92%					

[a] Conditions: (A) 1 mol % $Pd(dba)_2$, 1 mol % Q-phos; (B) 2 mol % $Pd(dba)_2$, 2 mol % Q-phos; (C) 3 mol % $Pd(dba)_2$, 3 mol % Q-phos; (D) 1 mol % $\{[P(t\text{-}Bu)_3]PdBr\}_2$, 1.05 equiv of KH. [b] Isolated yields (average of two runs) for reactions of 0.5 mmol of bromoarene in 5 mL of THF.

(88) The lithium enolate of diethylacetamide reacted in higher yields than the lithium enolate of dimethylacetamide. Culkin, D. A.; Hartwig, J. F., unpublished results.

couplings with bromoarenes occurred at room temperature, although a few examples required heating at 70 °C to occur to completion.

Like the reactions of *N*,*N*-diethylacetamide, the reaction of *N*,*N*-diethylpropionamide occurred with electron-neutral, electron-rich, or electron-poor aryl halides. These couplings also occurred with ortho-substituted bromoarenes, including those containing relatively minor electronic perturbations by the substituent in the ortho position (entry 3) and those containing electron-donating (entry 4) or -withdrawing groups (entry 5) at the ortho position. The coupling of *N*,*N*-diethylpropionamide also occurred selectively to replace the bromide of 4-chlorobromobenzene and 2-fluorobromobenzene.

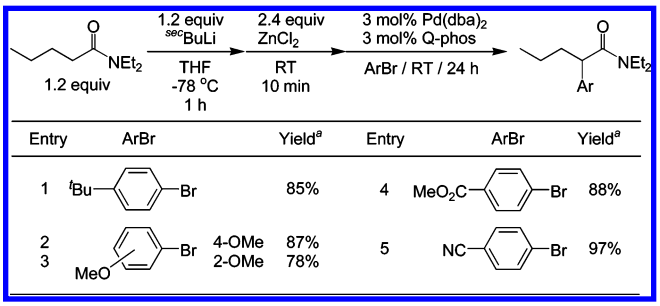
The couplings of *N*,*N*-diethylpropionamide occurred with bromoarenes, such as 4-bromobenzonitrile and 4-bromonitrobenzene, that contained functionality that is intolerant of the highly basic alkali metal amide enolates. In addition, the reaction occurred with 4-bromophenol and 4-bromoaniline by the procedure involving initial deprotonation of the protic functional group of the bromoarene with KH. Like the reaction of 4-bromophenol and 4-bromoaniline with *N*,*N*-diethylacetamide, the reaction of these substrates with *N*,*N*-diethylpropionamide occurred in higher yield with the dimeric catalyst containing P(*t*-Bu)$_3$ as ligand than with the catalyst generated from Q-phos.

At the same time, the scope of the coupling of *N*,*N*-diethylpropionamide was slightly narrower than the scope of the coupling of the less hindered *N*,*N*-diethylacetamide. The largest differences were observed for reactions of the two enolates with 4-bromoacetophenone and bromomesitylene. In contrast to the reaction of *N*,*N*-diethylacetamide with 4-bromoacetophenone, which occurred in high yield, the reaction of the zinc enolate of *N*,*N*-diethylpropionamide with 4-bromoacetophenone led to quenching of the enolate by the acidic hydrogen, and no product from coupling was observed by GC−MS. Also, while the reaction of *N*,*N*-diethylacetamide with bromomesitylene occurred in high yield, the reaction of the more hindered zinc enolate of *N*,*N*-diethylpropionamide with bromomesitylene did not occur.

One can also compare the reactions of the zinc propionamides generated from quenching of the lithium enolates to those of the zinc propionamides generated from α-bromo amides. The reactions of the zinc enolates generated from the α-bromo amide were somewhat faster, but the reactions of the zinc enolates generated by quenching of the alkali metal enolate occurred with broader scope. For example, the arylation of the zinc enolate generated from the α-bromopropionamide and activated zinc did not occur in high yield with bromoarenes containing cyano, nitro, or keto groups or with bromopyridines, but the arylation of the zinc enolate generated by quenching the lithium enolate with zinc chloride occurred in high yield with each of these types of aryl and heteroaryl bromides.

D. Coupling of the Zinc Enolate of *N*,*N*-Diethylpentanamide Generated via the Alkali Metal Enolate. Because the scope of the coupling process depended on the steric properties of the enolate, we determined whether higher homologues of *N*,*N*-diethylpropionamide would undergo the arylation process in the same fashion as *N*,*N*-diethylpropionamide. To do so, we conducted a few representative reactions of *N*,*N*-diethylpentanamide (Table 7). The zinc enolate of this amide underwent the coupling process in yields that were comparable to those of

Table 7. Arylation of the Zinc Enolate of *N*,*N*-Diethylpentanamide



Entry	ArBr	Yield[a]	Entry	ArBr	Yield[a]
1		85%	4		88%
2		4-OMe 87%	5		97%
3		2-OMe 78%			

[a] Isolated yields (average of two runs) for reactions of 0.5 mmol of bromoarene in 5 mL of THF.

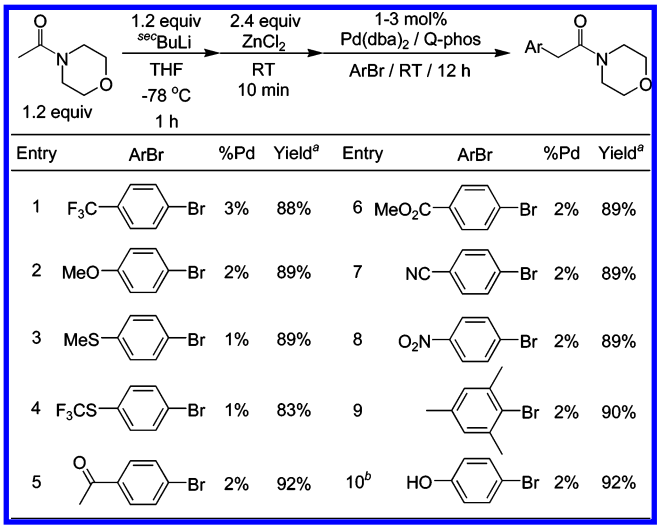
reactions of *N*,*N*-diethylpropionamide. With procedures to generate the zinc enolate that are essentially identical to those used to generate the enolate of *N*,*N*-diethylpropionamide and with 3 mol % of the palladium catalyst ligated by Q-phos, the coupling of *N*,*N*-diethylpentanamide with electron-neutral (entry 1), electron-rich (entries 2 and 3), and electron-poor bromoarenes (entries 4 and 5) occurred in high yield. Like the reactions of the propionamide enolate, cross-coupling occurred without reaction at an ester or nitrile functional group bound to the bromoarene, and the reaction occurred with a bromoarene containing an ortho substituent.

3. Coupling of the Enolates of Morpholine Amides. Weinreb amides are commonly used to generate ketones or aldehydes from compounds at the carboxylic acid oxidation level.[89,90] Thus, the α-arylation of a Weinreb amide or the equivalent would allow the synthesis of a variety of α-aryl carbonyl derivatives. Although the direct α-arylation of aldehydes has been reported,[91,92] the yields are modest with the most accessible catalysts. Thus, a route to an α-aryl aldehyde by way of an appropriate amide would be valuable. In addition, the α-arylation of an appropriate amide would allow the synthesis of certain α-aryl ketones that are inaccessible or that are formed in modest yield from direct α-arylation of an alkali metal ketone enolate. For example, ketones with particularly acidic α-hydrogens, such as α-aryl ketones,[93] undergo arylation at the position that forms the thermodynamically more stable enolate.[93,94] In other cases, when the difference in acidity is not large, the α-arylation occurs at the less hindered of the two possible enolates.[93] If the sizes of the two substituents of the ketone are similar, regioisomeric mixtures can result.[93] Further, reactions of alkali metal enolates of ketones can lack the functional group tolerance of reactions of other main group enolates, and reactions of the alkali metal enolates of methyl ketones can form products from diarylation.[93,95]

Unfortunately, the enolates of Weinreb amides are unstable.[96] Lithium enolates of Weinreb amides are known to decompose to form formaldehyde even at −78 °C.[96] We found that reaction of α-bromo Weinreb amides with activated zinc yielded products

(89) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(90) Sibi, M. *Org. Prep. Proc. Int.* **1993**, *25*, 15.
(91) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101.
(92) Lavallo, V.; Canac, Y.; Prasang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705.
(93) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
(94) Diarylation of methyl alkyl ketones occurs predominantly by diarylation of the methyl group, rather than monoarylation of the methyl and methylene positions. Lee, S.; Hartwig, J. F., unpublished results.
(95) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.
(96) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269.

Table 8. Arylation of the Zinc Enolate of Morpholine Acetamide



Entry	ArBr	%Pd	Yield[a]	Entry	ArBr	%Pd	Yield[a]
1	F_3C–Br	3%	88%	6	MeO_2C–Br	2%	89%
2	MeO–Br	2%	89%	7	NC–Br	2%	89%
3	MeS–Br	1%	89%	8	O_2N–Br	2%	89%
4	F_3CS–Br	1%	83%	9	Br	2%	90%
5	O, Br	2%	92%	10[b]	HO–Br	2%	92%

[a] Isolated yields (average of two runs) for reactions of 0.5 mmol of bromoarene in 5 mL of THF. [b] Reaction was conducted at 70 °C with 1 mol % $\{[P(t\text{-}Bu)_3]PdBr\}_2$ and 1.05 equiv of KH.

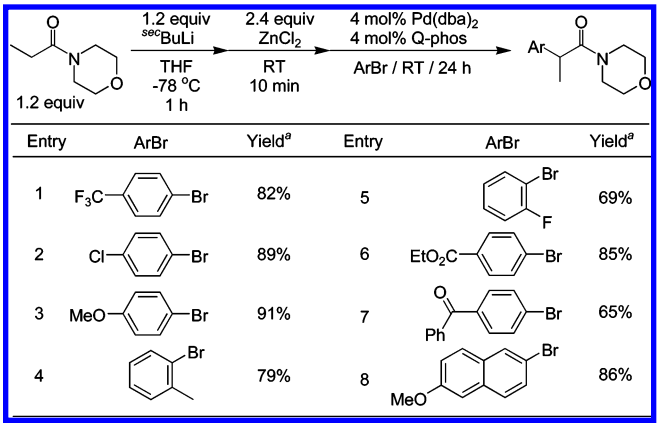
from reduction of the N−O bond, as determined by GC−MS. Thus, we sought to conduct the α-arylation with an analog of a Weinreb amide that would be stable as the alkali metal or zinc enolate. Because morpholine amides are known to undergo functional group interconversions that are similar to those of Weinreb amides,[97−99] we studied the α-arylation of morpholine amides.

A. Coupling of the Zinc Enolate of Morpholine Acetamide. Table 8 summarizes the reactions of morpholine acetamide. These reactions were conducted under conditions that were essentially identical to those of the reactions of *N*,*N*-dimethylacetamide involving generation of the enolate from *sec*-butyllithium at low temperature and quenching of the enolate at room temperature. Although *sec*-butyllithium could act as a nucleophile to generate a ketone instead of the desired enolate, morpholine acetamide did undergo deprotonation to form the desired enolate.

The palladium-catalyzed α-arylation of morpholine acetamide occurred in high yields with 1−3 mol % of palladium catalyst precursor and Q-phos ligand. Similar to reactions of *N*,*N*-dimethylacetamide, the reactions of the morpholine amide occurred with the electron-rich and electron-poor bromoarenes in entries 1 and 2 of Table 8, as well as the hindered bromoarene in entry 9. Moreover, these reactions occurred with methyl 4-bromobenzoate and 4-bromobenzonitrile without attack at the ester or nitrile, and they occurred with 4-bromonitrobenzene without interference from the nitro group. Finally, the reaction of 4-bromophenol occurred when the phenolic hydrogen was first deprotonated with KH. For reasons we do not understand, the analogous reaction with bromoaniline after deprotonation with KH did not occur, even though the coupling of bromoaniline under these conditions occurred with diethylacetamide and diethylpropionamide.

B. Coupling of the Zinc Enolate of Morpholine Propionamide. As illustrated in Table 9, the coupling of zinc enolates

Table 9. Arylation of the Zinc Enolate of Morpholine Propionamide



Entry	ArBr	Yield[a]	Entry	ArBr	Yield[a]
1	F_3C–Br	82%	5	Br, F	69%
2	Cl–Br	89%	6	EtO_2C–Br	85%
3	MeO–Br	91%	7	O, Ph, Br	65%
4	Br	79%	8	Br, MeO	86%

[a] Isolated yields (average of two runs) for reactions of 0.5 mmol of bromoarene in 5 mL of THF.

of morpholine propionamides occurred with similarly broad scope when the reactions were conducted with 4 mol % of palladium and Q-phos ligand. Reaction of morpholine propionamide occurred with aryl bromides of varied electronic properties and with varied functionality. The reaction occurred selectively at the bromide of 4-chlorobromobenzene and of 2-fluorobromobenzene. The zinc enolate of morpholine propionamide reacted at the bromide rather than the ester or phenacyl group. It also coupled with sterically hindered 2-bromotoluene. However, like the zinc enolate of *N*,*N*-diethylpropionamide, the zinc enolate of morpholine propionamide did not couple with 2,6-disubstituted bromomesitylene or with 4-bromoacetophenone, which possesses an accessible carbonyl group and enolizable hydrogens.

C. Coupling of the Zinc Enolate of Morpholine Isobutyramide. Finally, we investigated conditions to couple the enolates of α,α-disubstituted morpholine amides. We were unable to generate the appropriate enolate by deprotonation of morpholine isobutyramide and quenching with zinc chloride. However, we did generate this zinc enolate from the α-bromo amide, just as we generated the similarly hindered zinc enolate of *N*,*N*-dimethylisobutyramide from *N*,*N*-dimethyl-α-bromoisobutyramide. Thus, the Reformatsky reagent of morpholine isobutyramide generated in situ from the α-bromo amide and activated zinc coupled with a variety of aryl bromides and heteroaryl bromides in high yield at room temperature to 70 °C. These results are summarized in Table 10. The scope of the couplings of the enolate of morpholine isobutyramide, like that of the couplings of *N*,*N*-dimethylisobutyramide, was narrower than for the couplings of morpholine propionamide and acetamide. Coupling did not occur with bromoarenes containing functionality with enolizable hydrogens, free hydroxyl groups, or free amino groups. Moreover, the coupling did not occur with ortho-substituted bromoarenes. Yet, the reaction did occur with 2-bromopyridine and 3-bromothiophene.

4. Evaluation of the Basicity of the Zinc Enolates in the Coupling Process. In addition to demonstrating the ability of zinc enolates to increase the scope of the coupling of amide enolates, we also sought to determine the stereochemical consequences of conducting the α-arylation reactions with less basic amide enolates. In several contexts, one would wish to conduct the coupling process to create or preserve an enolizable

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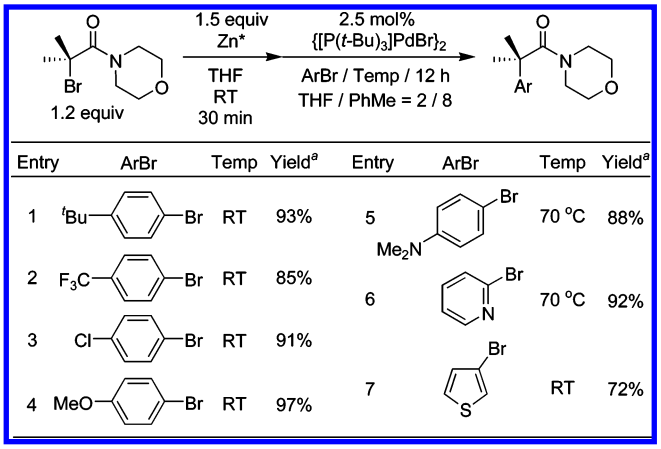
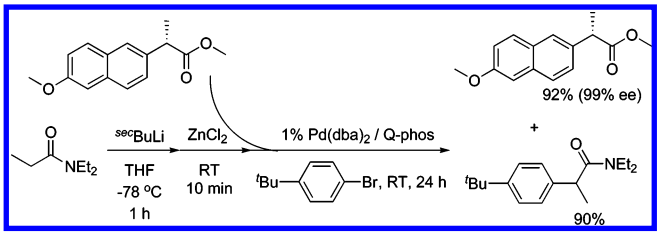
Table 10. Arylation of the Reformatsky Reagent of Morpholine Isobutyramide



[a] Isolated yields (average of two runs) for reactions of 0.5 mmol of bromoarene in mixed solvents of 1.2 mL of THF and 4.8 mL of toluene.

Scheme 2



stereocenter. For example, the electrophilic partner could contain an enolizable stereocenter, and reaction with an alkali metal enolate would lead to racemization of this stereocenter. Alternatively, one might desire to conduct an enantioselective, diastereoselective, or auxiliary-controlled stereoselective α-arylation. Because the product of α-arylation is more acidic than the starting carbonyl compound, racemization of any new tertiary stereocenter would occur if an alkali metal enolate were used as reactant.

To test directly the rate of proton transfer to and from the α-position of carbonyl groups during the α-arylation of zinc enolates, we conducted the α-arylation of the zinc enolate of *N*,*N*-diethylpropionamide in the presence of an ester with enolizable hydrogens. The reaction of the zinc enolate of *N*,*N*-diethylpropionamide with 4-bromo-*tert*-butylbenzene was conducted in the presence of the methyl ester of (*S*)-Naproxen (Scheme 2). The enolate was generated with *sec*-BuLi and quenched with $ZnCl_2$ at room temperature prior to the addition of the ester probe. The α-aryl propionamide product was formed in high yield, and the (*S*)-enantiomer of the methyl ester was recovered in 92% yield and in 99% ee. This result implies that proton transfer involving the zinc enolates is much slower than the coupling process. This result also implies that an appropriate catalyst or auxiliary could lead to asymmetric α-arylations of zinc propionamides and that diastereoselective α-arylations of zinc amides would generate products with kinetically controlled relative stereochemistry.

Conclusions and Comments on the Relationship to Classic Coupling Procedures

The scope of cross-coupling reactions of aryl, vinyl, and alkyl nucleophiles has been improved during the past decades by the development of procedures that replace the original reactions of organolithium and organomagnesium reagents[100,101] with reactions of organozinc[102,103] and organoboron reagents.[103−105] Although the coupling of enolate nucleophiles has been developed only recently, we have begun to show that the scope of these coupling processes can also be broadened dramatically by the use of enolates that are less basic than alkali metal enolates. To date, we have been unable to conduct couplings with boron enolates that would parallel the classic Suzuki reaction, but we have reported in communication form that reactions of aryl halides occur with some zinc enolates of esters. Now, we have shown that a wide range of reactions of aryl and vinyl bromides with zinc enolates of amides occur, and this development draws some parallels to the advantages of Negishi couplings of aryl, vinyl, and alkyl zinc reagents over Kumada couplings with more basic Grignard reagents.

Considering the high functional group tolerance of zinc enolates, the use of relatively nonpolar solvents for the coupling of zinc enolates, and the high yields and absence of diarylation products from the reactions of zinc amide enolates, we anticipate that these procedures will be a valuable contribution to the scope of coupling processes. We have shown in the current work (1) that the reactions of aryl halides with zinc amide enolates occur with less catalyst than reactions of alkali metal enolates; (2) that the coupling of zinc amide enolates can be conducted with hindered monophosphines that allow faster oxidative addition of electron-rich bromoarenes and coupling reactions at room temperature; (3) that the scope of the reactions of zinc amide enolates encompasses substrates with functionality that does not tolerate a strongly basic or nucleophilic enolate, such as ketones with enolizable hydrogens, nitriles, esters, and nitro groups; (4) that the reactions of zinc amide enolates form only products from monoarylation of the enolate; and (5) that the coupling of zinc amide enolates is faster than proton transfer between the zinc amide enolate and the α-carbon of an ester. These generalizations apply to reactions of zinc enolates that are generated from α-bromo esters and to reactions of zinc enolates that are generated by quenching of alkali metal amides with zinc halides.

Experimental Section

General Procedure for the Arylation of Isolated Reformatsky Reagents of Amides. In the drybox, a solution of $Pd(dba)_2$ (11.5 mg, 0.0200 mmol), Q-phos (14.3 mg, 0.0200 mmol), and aryl halide (1.00 mmol) in 8 mL of dioxane was added to a round-bottom flask containing a stirred solution of the isolated Reformatsky reagent generated from the α-bromo amide (1.20 mmol) in dioxane (10 mL). The flask was sealed with a rubber septum and removed from the drybox. The reaction mixture was stirred at room temperature and monitored by GC analysis. Upon consumption of the aryl halide, the reaction mixture was poured into 40 mL of saturated aqueous NH_4Cl and extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel. The reaction conditions and results are shown in Table 1.

General Procedure for the α-Arylation of Amides Starting from 2-Bromo-*N*,*N*-dimethylpropanamide. The reactions were conducted under a nitrogen atmosphere in a drybox. Activated zinc dust (0.750

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mmol) was suspended in THF (0.5 mL) in a 10 mL round-bottom flask. To this mixture was added dropwise a solution of 2-bromo-*N*,*N*-dimethylpropanamide (0.600 mmol) dissolved in THF (0.7 mL), and the flask was capped with a rubber septum. The reaction mixture was stirred at room temperature for 30 min. To this heterogeneous solution was added a solution of the aryl bromide (0.500 mmol) and $\{[P(t\text{-}Bu)_3]PdBr\}_2$ (12.5 μmol) in 4.8 mL of toluene. The flask was removed from the drybox. The resulting solution was stirred for 12 h. The reaction mixture was loaded directly onto a silica gel column and separated by chromatography.

General Procedure for Arylation of Zinc Enolates Generated from 2-Bromo-*N*,*N*-diethylacetamide and 2-Bromo-*N*,*N*-diethylpropanamide with Rieke Activated Zinc. The reactions were conducted under a nitrogen atmosphere in a drybox. Rieke activated zinc dust (49.0 mg, 0.750 mmol) was suspended in THF (1.0 mL) in a 4 mL screw-capped vial. To this mixture was added dropwise the α-bromoamide (0.550 mmol) by syringe, and the vial was capped. The reaction mixture was stirred at room temperature for 30 min. To the resulting heterogeneous solution was added a solution of aryl bromide (0.500 mmol), $Pd(dba)_2$ (2.8 mg, 5.00 μmol), and Q-phos (3.6 mg, 5.00 μmol) in THF (1.0 mL). The vial was sealed with a cap containing a polytetrafluoroethylene septum and removed from the drybox. The resulting solution was stirred for 6 h. After this time, the solvent was evaporated, the residue was dissolved in methylene chloride with application of sonication, and this methylene chloride solution was loaded directly onto a silica gel column and purified by chromatography.

General Procedure for the α-Arylation of Amides from Alkali Metal Enolates and $ZnCl_2$. The reactions were conducted under a nitrogen atmosphere. In a 10 mL round-bottom flask sealed with a rubber septum was dissolved *sec*-butyllithium (430 μL, 0.600 mmol, 1.4 M in cyclohexane) with THF (4 mL) at −78 °C. To this solution was added amide (0.600 mmol) dropwise at −78 °C. The resultant mixture was stirred for 1 h at −78 °C. The solution of the enolate was allowed to warm to room temperature. The septum was fastened to the flask with electrical tape, and the flask was brought into a drybox. To the solution of enolate was added zinc chloride (163.5 mg, 1.20 mmol). The resulting solution was stirred for 10 min at room temperature. To this solution was added a solution of 0.500 mmol of aryl bromide, $Pd(dba)_2$, and Q-phos in THF (1 mL). The amounts of catalyst components are provided in the tables in the Results and Discussion section. The resulting reaction mixture was stirred for 24 h at room temperature. After this time, the solvent was evaporated, the residue was dissolved in methylene chloride with application of sonication, and this methylene chloride solution was loaded directly onto a silica column. Conditions for elution are provided along with the spectroscopic and analytical data for each product.

General Procedure for the α-Arylation with 4-Bromophenol and 4-Bromoaniline. The reactions were conducted under a nitrogen atmosphere. *sec*-Butyllithium (430 μL, 0.600 mmol, 1.4 M in cyclohexane) was dissolved in THF (4 mL) in a 10 mL round-bottom flask sealed with a rubber septum at −78 °C. To this solution was added the amide (0.600 mmol) dropwise at −78 °C. The resulting mixture was stirred for 1 h at −78 °C. The solution of the enolate was allowed to warm to room temperature. The septum was fastened to the flask with electrical tape, and the flask was brought into a drybox. To the solution of enolate was added zinc chloride. The resulting solution was stirred for 10 min at room temperature. In separate reaction vessel in a drybox, aryl halide (0.500 mmol) in THF (1.0 mL) was slowly added to KH (0.525 mmol). Gas evolution occurred immediately. The reaction mixture was stirred for 10 min at room temperature. This suspension was mixed with $\{[P(t\text{-}Bu)_3]PdBr\}_2$. The amount of catalyst in each reaction is provided in the tables in the Results and Discussion section. To this resultant suspension was added the THF solution of zinc enolate. The resulting reaction mixture was stirred for 12 h at room temperature. After this time, the reaction mixture was diluted with Et_2O (30 mL). The resulting solution was washed with saturated NH_4Cl (aqueous) (25 mL) and back-extracted with Et_2O (3 × 30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was then purified by flash column chromatography on silica gel. Conditions for elution are provided in the Supporting Information, along with the spectroscopic and analytical data for each product.

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Supporting Information Available: Full Experimental Section, including characterization of all reaction products and demonstration of purity. This material is available free of charge via the Internet at http://pubs.acs.org.

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