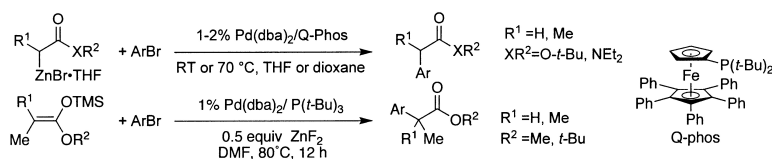


Palladium-Catalyzed α -Arylation of Esters and Amides under More Neutral Conditions

Takuo Hama, Xiaoxiang Liu, Darcy A. Culkin, and John F. Hartwig

J. Am. Chem. Soc., **2003**, 125 (37), 11176-11177 • DOI: 10.1021/ja036792p • Publication Date (Web): 21 August 2003

Downloaded from <http://pubs.acs.org> on March 29, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 18 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



Palladium-Catalyzed α -Arylation of Esters and Amides under More Neutral Conditions

Takuo Hama, Xiaoxiang Liu, Darcy A. Culkin, and John F. Hartwig*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

Received June 19, 2003; E-mail: John.Hartwig@yale.edu

The palladium-catalyzed reaction of aryl halides with alkali metal enolates has become a convenient synthetic method.^{1–4} These procedures are simple to conduct, but a number of drawbacks result from the basic reaction conditions. Reactions of substrates bearing nitro, cyano, carboxyl, and keto groups, which react with strong bases and nucleophiles, occurred in low yield. Also, coupling at the more hindered of two enolizable positions was not possible. Moreover, the basic conditions limit control of stereochemistry. Products with new tertiary stereocenters would be racemized because of the greater acidity of the product, and substrates with auxiliary, base-sensitive stereocenters can undergo racemization. Finally, the strong base required to generate amide enolates has limited the scope of the coupling of amides even with unfunctionalized bromoarenes.^{5,6}

We report two procedures for the α -arylation of carbonyl compounds under conditions that are more neutral than those for reactions of aryl halides with alkali metal enolates. The first procedure involves the use of zinc enolates and rests upon the development of catalysts bearing the hindered pentaphenylferrocenyl di-*tert*-butylphosphine (Q-phos)^{7,8} and the highly reactive dimeric Pd(I) complex $\{P(t-Bu)_3\}PdBr_2$.⁹ Previous studies on the cross-coupling of zinc enolates included reactions of only acetate enolates with a small set of aryl halides in modest yields.^{10–15} The second procedure involves palladium-catalyzed reactions of silyl ketene and silyl ketimine acetals in the presence of zinc fluoride cocatalyst. Previous palladium-catalyzed couplings of these enolates with aryl halides were conducted with tin fluoride additives to generate the tin enolates^{16–18} or with suprastoichiometric amounts of both enolate and copper fluoride additive.¹⁹ Tin halides generate toxic byproducts, and an excess of copper complicates product separation. These previous reports included only acetate enolates.

Palladium catalysts bearing hindered alkyl phosphines catalyzed the coupling of Reformatsky reagents prepared from activated zinc and α -bromo esters with a wide variety of base-sensitive substrates, as summarized in Table 1. The chemistry with Reformatsky reagents in Table 1 was conducted in the presence of 1 or 2 mol % of a combination of Pd(dba)₂ and Q-phos or 0.5 mol % $\{P(t-Bu)_3\}PdBr_2$. In most cases, both catalysts provided good yields, but, with the exception of aryl halides with acidic protons, the catalyst with Q-phos created a more general process. The broad scope and high yields were not obtained with triarylphosphine catalysts.^{12,13}

Our study on the coupling of zinc ester enolates focused on the reactions of aryl and heteroaryl halides that did not undergo palladium-catalyzed couplings with alkali metal enolates.^{20,21} For example, bromonitrobenzenes, bromobenzonitriles, aryl halides with enolizable hydrogens, and aryl halides of electrophilic ketones did not undergo palladium-catalyzed coupling with lithium acetate or propionate enolates. However, coupling of these aryl bromides with the Reformatsky reagent of *tert*-butyl acetate or propionate occurred in high yield at room temperature (entries 1, 2, 5–9, 11–13). Reactions of zinc enolates with aryl halides bearing protic

Table 1. Reactions of Reformatsky Reagents with Bromoarenes Bearing Potentially Reactive Functional Groups

Entry	ArBr	R ¹	XR ²	Cond. ^a	Temp.	Time	Yield ^d
1		R ³ =Me	Me	O- <i>t</i> -Bu	A	RT	4 h 87%
2		Me	Me	O- <i>t</i> -Bu	B	RT	4 h 81%
3		R ³ =Et	H	NEt ₂	C	RT	6 h 94%
4		Me	Me	NEt ₂	C	RT	6 h 95%
5		R ³ =Ph	H	O- <i>t</i> -Bu	A ^b	RT	4 h 72%
6		R ³ =Ph	Me	O- <i>t</i> -Bu	A	70°C	4 h 89%
7		R ³ =Et	H	O- <i>t</i> -Bu	A	RT	4 h 94%
8		4-NO ₂	H	O- <i>t</i> -Bu	A	RT	4 h 96%
9		2-NO ₂	H	O- <i>t</i> -Bu	A	RT	4 h 87%
10		4-NO ₂	Me	NEt ₂	C	RT	6 h 97%
11		2-CN	H	O- <i>t</i> -Bu	A	RT	4 h 91%
12		2-CN	H	O- <i>t</i> -Bu	B	RT	4 h 81%
13		2-CN	Me	O- <i>t</i> -Bu	A ^b	RT	4 h 85%
14		4-CN	H	NEt ₂	C	RT	6 h 86%
15		4-OH	H	O- <i>t</i> -Bu	D	RT	4 h 91%
16		4-OH	Me	O- <i>t</i> -Bu	D	RT	4 h 95%
17		2-OH	H	O- <i>t</i> -Bu	D	RT	4 h 83%
18		H	Me	O- <i>t</i> -Bu	D	RT	24 h 85%
19		Me	Me	O- <i>t</i> -Bu	B ^c	RT	12 h 70%
20		Me	Me	O- <i>t</i> -Bu	D	RT	24 h 66%
21		4-Br	H	O- <i>t</i> -Bu	A	70°C	4 h 79%
22		3-Br	H	O- <i>t</i> -Bu	A	70°C	4 h 90%
23		3-Br	Me	O- <i>t</i> -Bu	A	70°C	4 h 91%
24		H	Me	NEt ₂	C	RT	6 h 92%
25		Me	Me	NEt ₂	C	RT	6 h 88%
26		4-OMe	H	NEt ₂	C	RT	6 h 91%
27		3-OMe	Me	NEt ₂	C	RT	6 h 88%
28		H	Me	NEt ₂	C	RT	6 h 91%
29		Me	Me	NEt ₂	C	RT	6 h 88%

^a Standard conditions: (A) 1 mol % Pd(dba)₂, 1 mol % Ph₅FcP(*t*-Bu)₂, 1.1 equiv of enolate, THF; (B) 0.5 mol % $\{P(t-Bu)_3\}PdBr_2$, 1.1 equiv of enolate, THF; (C) 2 mol % Pd(dba)₂, 2 mol % Ph₅FcP(*t*-Bu)₂, 1.2 equiv of enolate, dioxane; (D) 1.05 equiv of KH, 0.5 mol % $\{P(t-Bu)_3\}PdBr_2$, 1.1 equiv of enolate, THF. ^b 2 mol % Pd(dba)₂ and Q-phos were used. ^c 2 equiv of enolate. ^d Yields are for pure isolated material and are an average of two runs.

functionality (entries 15–20) also occurred if 2 equiv of the Reformatsky reagent was added or if 1 equiv of KH was added before the Reformatsky reagent. For example, most combinations of the two enolates and 2- or 4-bromophenol and 4-bromoaniline formed the α -aryl ester in high yield. In contrast to the reactions of alkali metal ester enolates,^{20,21} no products from diarylation of zinc acetate or propionate enolates were observed.

Reactions of halopyridines also did not form α -heteroaryl esters in previous work with lithium enolates of acetates or propionates.^{20,21} However, reaction of the corresponding zinc enolates with bromopyridines generated the products in high yields in several cases (entries 21–23). The Reformatsky reagent of *tert*-butyl acetate reacted with both 3- and 4-bromopyridine in high yield. Moreover, the zinc enolate of *tert*-butylpropionate coupled with 3-bromopyridine in high yield.

To test if the less basic conditions improved the scope and yields for the α -arylation of the amides, we conducted reactions of the

Table 2. Coupling of Silyl Ketene Acetals with Bromoarenes

ArBr	R ¹	yield ^a	ArBr	R ¹	yield ^a
	H	67%		H	67%
	H	80%		Me	88%
	Me	94%		Me	98%
	H	68%		H	76%
	Me	78%		Me	95%
	Me	99%		Me	91%
	H	75%		H	75%

^a Yields are for pure isolated material and are an average of two runs.

Reformatsky reagents generated from α -bromodiethylacetamide and α -bromodiethylpropionamide with bromoarenes. Indeed, coupling occurred with broad scope at room temperature (Table 1, entries 3, 4, 10, 14, 24–29). The reaction scope encompassed aryl halides, such as 4-bromobenzotrifluoride, 4-bromobenzonitrile, and the electron-rich bromoanisole, that failed to react in high yield with potassium amide enolates in the presence of palladium and BINAP.⁵ The zinc enolates formed none of the diarylation product that reduced yields of reactions of potassium enolates.⁵

Alkali metal enolates of propionamides reacted in low yields with all aryl halides in published work⁵ conducted with palladium catalysts bearing monodentate or bidentate ligands. However, coupling of the zinc enolate generated from α -bromodiethylpropionamide occurred in high yield at room temperature with a variety of aryl bromides, including those with electron-donating or potentially reactive, base-sensitive electron-withdrawing groups.

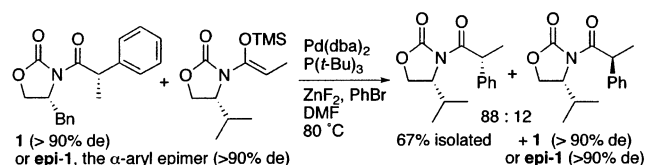
The second protocol resulted from conditions that improve the rate of transmetalation of silyl enolate without use of toxic tin additives or an excess of copper halide and enolate. Silicon enolates can be advantageous over Reformatsky reagents because they are prepared directly from the ester and they are even less basic than Reformatsky reagents. Silyl ketene acetals and silyl enol ethers react in the presence of Lewis acidic transition metal catalysts,^{22,23} but the rate for transmetalation of the enolate from the hard main group metal to soft late metals could be slow.

Yet, we found that the silyl ketene acetal of *tert*-butyl propionate or methyl isobutyrate reacted in high yield at 80 °C with bromoarenes to form the corresponding α -aryl esters in the presence of palladium catalysts ligated by $P(t\text{-Bu})_3$ and ZnF_2 as cocatalyst. Reaction yields were higher with zinc fluoride than with other zinc halides.

Coupling of the silyl ketene acetals with bromoarenes occurred with broad scope, as summarized in Table 2. Aryl halides containing enolizable hydrogens, as well as electrophilic and base-sensitive functionality, all reacted in high yield. Even substrates, such as methyl ketones, that underwent attack at the carbonyl group by zinc enolates faster than they underwent coupling, produced the α -aryl esters from reactions of silyl ketene acetals.

Palladium-catalyzed α -arylation of imides bearing chiral auxiliaries²⁴ would provide a method to prepare optically active α -aryl carbonyl compounds. In the presence of strong base at room temperature or above, this process would provide an equilibrium ratio of products. Moreover, the alkoxide base of the coupling chemistry cleaves the auxiliary from the enolate.²⁴

In contrast, reaction of the silyl ketimine acetal of the Evans auxiliary with phenyl bromide formed the coupled products in an 88:12 ratio of diastereomers and a 67% isolated yield of the major

Scheme 1

isomer. To determine if the more neutral conditions generated a kinetic ratio of diastereomers, we conducted the arylation of the silyl enolate of one imide in the presence of a diastereomerically pure α -aryl imide **1** and its epimer at the α -aryl position **epi-1** (Scheme 1). This reaction formed the same ratio of diastereomers as the reaction conducted without added α -aryl amide, and the stereochemistry of the added imides remained unaltered. Thus, the conditions for the α -arylation of the silyl enolates are neutral enough to prevent silyl group migration and epimerization of base-sensitive stereocenters.

In summary, two advances in catalyst and reaction design have significantly expanded the scope of the α -arylation of carbonyl compounds. Highly reactive catalysts based on Q-phos or Pd(I) dimers, in combination with zinc enolates or silicon enolates with ZnF_2 additive, allow the preparation of α -aryl esters and amides from substrates that bear functionality or stereochemistry that is sensitive to the basicity or nucleophilicity of alkali metal enolates. Further studies that exploit the broad scope and lack of racemization are in progress.

Acknowledgment. We thank the NIH-NIGMS (GM58108), Merck Research Laboratories, and Johnson-Matthey for support.

Supporting Information Available: Reaction procedures and characterization of products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.
- Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.
- Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
- For a Highlight article, see: Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953.
- Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.
- Lee, S.; Hartwig, J. *J. Org. Chem.* **2001**, *66*, 3402.
- Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718.
- Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.
- Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746.
- Orsini, F.; Pelizzoni, F. *Synth. Commun.* **1987**, *17*, 1389.
- Orsini, F.; Pelizzoni, F.; Vallarino, L. M. *J. Organomet. Chem.* **1989**, *367*, 375.
- Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273.
- Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1977**, *132*, C17.
- Knochel, P.; Jones, P., Eds. *Organozinc Reagents*; Oxford University Press: New York, 1999.
- Negishi, E.-i. In *Metal Catalyzed Cross-coupling Reactions*; Stang, P. J., Ed.; Wiley-VCH: New York, 1998; Chapter 1.
- Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; Migita, T. *Chem. Lett.* **1982**, 939.
- Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242.
- Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831.
- Agnelli, F.; Sulikowski, G. A. *Tetrahedron Lett.* **1998**, *39*, 8807.
- Jørgensen, M.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557.
- Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996.
- Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357.
- Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 493.
- Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

JA036792P