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Pd–arylurea complexes for the Heck arylation of crotonic and cinnamic substrates

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ABSTRACT

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Liu and Guo reported¹ that *N*-phenylurea is an effective substitute for phosphine ligands in Pd-catalyzed processes such as Mizoroki-Heck² and Suzuki³ reactions. Our own experience has shown that the Liu-Guo ligand is superior even to efficacious, but costly, S-Phos⁴ in the Heck arylation of amino acid-derived olefins.⁵ As a consequence, we have become interested in evaluating the use of phenylureas as ligands in other Pd-mediated reactions. An opportunity in that sense arose when a need materialized for quantities of amino acids 1 (Fig. 1). These are special cases of 3.3-diarylalanines, which are of interest in peptide research⁶ and in medicinal chemistry,⁷ and that may be prepared enantioselectively by phase-transfer alkylation of glycine enolates,⁸ or by Evans azidation⁹ of acids **2**.¹⁰ The latter, or their esters, are available by hydrogenation of α,β -unsaturated congeners,¹¹ which can be reached by Heck arylation of cinnamic substrates. Such a reaction is much less facile than that of simple acrylate systems (vide infra); it thus seemed interesting to evaluate the Liu-Guo complex in such a context.

The effectiveness of the $Pd(OAc)_2$ *N*-phenylurea system in the Heck arylation of ethyl cinnamate was comparable to that of the $Pd(OAc)_2$ -PPh₃ catalyst,¹² but in either case yields were moderate. Moreover, the Liu–Guo complex performed adequately only in donor solvents such as DMF or NMP (the solvent of choice) and, interestingly, only with deactivated, electron-rich aryl iodides such as **3** (Table 1). Activated, electron-deficient halides, for example, methyl 4-iodobenzoate, failed to react and were recovered virtu-

ally unchanged, even though they do arylate plain acrylate esters in excellent yield under identical conditions.¹

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A catalyst consisting of the 1:2 complex of $Pd(OAc)_2$ (1 mol %) with N-(4-carbethoxy)-phenylurea pro-

motes the Heck arylation of a range of crotonic and cinnamic substrates, including aldehydes, ketones,

esters, and nitriles, with electron-rich-but not electron-deficient-aryl iodides.

The influence of heretofore unexplored electronic factors on the performance of the ligand was examined with 4-carbethoxy-phenyl urea ('CEPU') and 4-methoxyphenyl urea in lieu of phenylurea. The yield of **4** increased from 46% to 75% with CEPU as the ligand. Further work revealed that 1 mol % of the 1:2 complex of Pd(OAc)₂ with CEPU is generally effective in the arylation of cinnamic and crotonic esters, aldehydes, and nitriles, as well as chalcone, but, again, only with electron-rich arvl iodides. Tables 2 and 3 summarize the results of Heck reactions of oxygen- and nitrogen-substituted aryl iodides promoted by the Pd(OAc)₂-CEPU complex. Yields were generally good to excellent, except when 4-(pivaloyloxy)-iodobenzene was used as the halide. Reactions of the latter returned the free phenolic forms of products 6g-l.¹³ Control experiments showed that reactions carried out with unprotected 4-iodophenol yielded no Heck product, even though the halide was consumed. The lower yields obtained with 4-(pivaloyloxy)-iodobenzene must thus be due to premature depivaloylation of a portion of the halide and consumption of the resultant iodophenol through side reactions. In accord with precedent,¹⁴ most Heck products were obtained as mixtures of geometric isomers, the dominant one being that in which the entering Ar group and the









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Table 1

Liu-Guo arylation of ethyl cinnamate



Entry	Catalyst ^a	Solvent	Yield ^b	E/Z^{c}
a	a	DMF	35	2.6:1
b	b	DMF	33	2.5:1
с	с	DMF	31	2.6:1
d	d	NMP	46	2.6:1
e	e	NMP	29	2.1:1
f	f	NMP	75	2.1:1

^a Catalyst (a) 5 mol % [Pd(OAc)₂(PPh₃)₂]; (b) 1 mol % [Pd(OAc)₂(PPh₃)₂]; (c) 1 mol % Pd(OAc)₂·[*N*-phenylurea]₂; (d) 1 mol % Pd(OAc)₂[*N*-(4-meth-oxyphenyl)urea]₂; (e) 1 mol% Pd(OAc)₂[*N*-(4-carbethoxyphenyl)urea]₂.

^b Yields of products purified by flash chromatography.

^c Proton NMR.

Table 2

Heck arylation of cinnamic and crotonic substrates with oxygen-substituted aryl iodides



Entry	\mathbb{R}^1	R ²	EWG	Yield ^a	$E/Z^{\mathbf{b}}$
a	MeO	Ph	COOEt	75	2.1:1
b	MeO	Me	COOMe	97	1.0:1
с	MeO	Me	CHO	76	3.0:1
d	MeO	Me	CN	92	3.5:1
e	MeO	Ph	CHO	84	2.6:1
f	MeO	Ph	COPh	66	2.2:1
g	PivO ^c	Me	COOMe	45	1.0:1
h	PivO ^c	Ph	CHO	47	1.6:1
i	PivO ^c	Me	CN	56	5.5:1
j	PivO ^c	Me	CHO	36	7.3:1
k	PivO ^c	Ph	COOEt	28	1.3:1
1	PivO ^c	Ph	COPh	35	1.7:1

 $^{\rm a}\,$ Yields of products purified by flash chromatography, except for entry i. $^{\rm b}\,$ Proton NMR.

^c Reactions of 4-pivaloylophenyl iodide returned the free phenolic form of the product. The stated yields are those of the free phenols. For ease of purification and characterization, the latter were converted back into the pivalate ester.

electron-withdrawing group (EWG) are *trans*. The results of Table 4, underscore the fact that plain iodobenzene reacted normally to give the expected products in 55–70% yield, but that, as indicated earlier, aryl bromides reacted poorly, while an aryl chloride failed altogether to react.

Scheme 1 shows some reactions of cinnamate esters **11–13**, which were made in high yield by arylation of *tert*-butyl acrylate by the Liu–Guo procedure,¹ or by the use of the Pd/CEPU system described herein. Thus, just as the original Liu–Guo catalyst, the Pd/CEPU system performs normally in the Heck reaction of simple acrylate esters with aryl halides carrying electron-withdrawing

Table 3

Heck arylation of cinnamic and crotonic substrates with nitrogen-substituted aryl iodides



Entry	\mathbb{R}^1	\mathbb{R}^2	EWG	Yield ^a	$E/Z^{\mathbf{b}}$
a	Me ₂ N	Ph	COOEt	51	4.0:1
b	Me_2N	Me	COOMe	41	1.0:1
с	Me_2N	Me	CN	84	2.9:1
d	Me_2N	Me	CHO	71	5.3:1
e	Me_2N	Ph	CHO	98	2.3:1
f	Me_2N	Ph	COPh	99	2.0:1
g	BOCHIN	Me	COOMe	51	1.0:1
h	BOCHIN	Ph	CN	99	2.7:1
i	BOCHIN	Me	CHO	50	92:1
j	BOCHIN	Ph	CHO	99	3.0:1
k	BOCHIN	Ph	COOEt	71	3.0:1
1	BOCHIN	Ph	COPh	77	3.0:1

^a Yields of products purified by flash chromatography.

^b Proton NMR.

Table 4

Heck arylation of cinnamic and crotonic substrates with miscellaneous aryl halides



Entry	R ¹	Х	\mathbb{R}^2	EWG	Yield ^a	$E/Z^{\mathbf{b}}$
a	Н	Ι	Ph	COOEt	72	_
b	Н	Ι	Me	COOMe	57	1.0:1
с	Н	Ι	Me	СНО	34	6.3:1
d	Н	Ι	Ph	СНО	80	_
e	Н	Br	Ph	COOEt	15	_
f	MeO	Br	Ph	COOEt	12	1.0:1
g	Me ₂ N	Br	Ph	COOEt	17	1.7:1
ĥ	Me_2N	Cl	Ph	COOEt	nr	-

^a Yields of products purified by flash chromatography.

^b Proton NMR.



Scheme 1. Heck arylation of substituted cinnamic esters.

Table 5

Comparison of Heck arylation by the Buchwald method versus the $\mbox{Pd}(\mbox{OAc})_2\mbox{-CEPU}$ procedure



Entry	R	Ar	EWG	Product	Yield ^{b,c}
a b c d	4-Me ₂ NC ₆ H ₄ 4-MeOC ₆ H ₄ Me Me	$\begin{array}{l} 4\text{-}Me_2NC_6H_4\\ 4\text{-}MeOC_6H_4\\ 4\text{-}MeOC_6H_4\\ Ph \end{array}$	COO <i>t-</i> Bu COO <i>t-</i> Bu CN CHO	19 15 6d 10c	70 (50) 41 (54) 77 ^d (92) – (34)
e	Me	4-MeOC ₆ H ₄	CHO	6e	- (76)

^a3% Pd(OAc)₂, 1 equiv Cy₂NMe, 1.1 equiv Ar–I, DMA, 85 °C, 16 h (Ref. 20).

^b Yields of products purified by flash chromatography.

^c Yields in parentheses are those of products obtained by the CEPU procedure.

^d This reaction also afforded the product of homocoupling of the aryl iodide, that is, 4,4'-dimethoxy-1,1'-biphenyl, in 19% yield.

groups, even though it fails to induce arylation of cinnamic/crotonic substrates with such halides.

Relative to alternative methods for the arylation of cinnamic/ crotonic systems, the Pd/CEPU procedure seems advantageous in terms of ease of preparation of the catalyst and-especially-scope with respect to the olefinic substrate. For instance, the arylation of cinnamic esters has been carried out with palladacycle catalysts,¹⁵ or Pd complexes of highly electron-rich¹⁶ or polydentate¹⁷ phosphines, possibly with microwave irradiation,¹⁸ or with supported Pd nanoparticles.¹⁹ A more practical, phosphine-free catalyst for this process has been described by Buchwald.²⁰ Relative to the Pd-CEPU complex, the Buchwald system exhibits a broader scope with respect to the aryl halide, in that it works well with aryl iodides and bromides carrying electron donating or electron-withdrawing groups, and it employs the aryl halide in only 10% excess relative to the olefinic substrate. Conversely, it requires more Pd (3 mol % vs 1 mol %), and it was demonstrated only with esters. This provided an incentive to examine the relative performance of the two catalytic systems. In our hands, the Buchwald procedure afforded 19 in higher yield relative to the CEPU method

Table 6

Heck arylation of cinnamal dehyde and chalcone by the Buchwald method versus the $\mbox{Pd}(\mbox{OAc})_2\mbox{-CEPU}$ procedure



Entry	Ar	EWG	Product and yield ^{b,c}	Yield of $20^{b,c}$
a	4-MeOC ₆ H ₄	CHO	6e 45 (84)	14 (-) ^d
b	Ph	CHO	10d 23 (80)	22 (-) ^d
с	4-MeOC ₆ H ₄	COPh	6f 58 (66)	38 (-) ^e

^a3% Pd(OAc)₂, 1 equiv Cy₂NMe, 1.1 equiv Ar–I, DMA, 85 °C, 16 h (Ref. 20). ^b Yields of products purified by flash chromatography.

^c Yields in parentheses are those of products obtained by the Pd/CEPU procedure.

^d Compounds **6e–20a** and **10d–20b** had similar chromatographic mobilities and were not separated: yields of individual products were calculated based on the ratio of the two (¹H NMR) in the material obtained after chromatographic purification of the crude reaction mixture.

^e The numbers given correspond to the yield of individual products, which in this case were readily separated by chromatography.



Scheme 2. Catalytic reduction of 15 and 19.

(70% vs 50%; Table 5), but it provided **15** in lower yield (41% vs 54%); furthermore, it was uniformly less satisfactory with other crotonic/cinnamic substrates. For instance, the arylation of crotononitrile proceeded to afford **6d** in 77% yield (vs 92% with the Pd–CEPU system, Table 5), but the reaction also afforded 4,4'-dimethoxy-1,1'-biphenyl, the product of homo-coupling of the aryl halide, in 19% yield relative to the starting halide. No such homo-coupling product was observed in CEPU-mediated reactions. It is worth noting that either system performed better than the Jiang-Cai catalyst²¹ (Pd on zeolites, 50% yield) in the arylation of crotononitrile. Chalcone and cinnamaldehyde did undergo arylation in moderate yield under Buchwald conditions, but they also yielded significant amounts of products of 'reductive Heck' reaction (Table 6).²² Such byproducts were not detected in arylation reactions carried out with the Pd–CEPU system.

The notoriously problematic arylation of crotonaldehyde²³ failed altogether with the Buchwald system, returning instead mixtures containing mostly the product of reductive Heck reaction, accompanied by unidentified byproducts (¹H NMR; Table 5). By contrast, the Pd–CEPU catalyst induced the formation of **6c**, **8d**, and **8i** in satisfactory yield. List²⁴ has described a variant of the Buchwald procedure that achieves the efficient arylation of crotonaldehyde and other enals, which however are employed in twofold molar excess with respect to the aryl halide. On the other hand, no indication is available regarding the performance of the List system with other olefinic systems. The same is true for a Pd(0)–NHC complex developed by Minnaard²⁵ (1.5 mol % of Pd) for the arylation of chalcones.²⁶ At this time, it would seem that the Pd(OAc)₂–CEPU system accepts a broader range of crotonic/cinnamic substrates than other known Heck catalysts.

On a final note, the catalytic reduction of products **15** and **19** occurred uneventfully (Scheme 2), thereby realizing our original objective.²⁷

In summary, this work shows that previously unexplored electronic effects can be harnessed to modulate the properties of arylurea ligands in Pd-mediated reactions. A Pd-arylurea complex for the Heck arylation of diverse crotonic and cinnamic systems in synthetically useful yield has thus resulted. Good results are generally observed with a diversity of such acceptors, most notably with crotonaldehyde. This catalytic system exhibits an unusual preference for deactivated, electron-rich aryl iodides. Studies centering on further applications of Pd-arylurea complexes are underway, and pertinent results will be disclosed in due course.

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Supplementary data

Supplementary data (experimental procedures, characterization data for new compounds, ¹H and ¹³C NMR spectra.) associated with this article can be found, in the online version, at http:// dx.doi.org/10.1016/j.tetlet.2013.01.077.

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