



Selective reactivity of electron-rich aryl iodides in the Heck arylation of disubstituted alkenes catalyzed by palladium–arylurea complexes



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ABSTRACT

A catalyst consisting of 1 mol % of the 1:2 complex of Pd(OAc)₂ with *N*-(4-carbomethoxyphenyl)urea promotes the Heck arylation of 2- or 3-substituted, conjugated esters, nitriles, aldehydes, and ketones (an uncharacteristically broad range of substrates), but only with electron-rich aryl iodides (an uncharacteristically narrow range of halides).

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1. Introduction

A recent communication from this group¹ describes the Mizoroki–Heck arylation² of crotonic and cinnamic substrates in the presence of a Liu–Guo-type³ catalyst consisting of 1 mol % of the 1:2 complex of Pd(OAc)₂ and *N*-[4-(carbomethoxy)]phenylurea (CEPU) in *N*-methyl-2-pyrrolidinone (NMP) as the solvent, and the presence of K₂CO₃ as the base. This catalytic system produces superior results relative to traditional Pd(PPh₃)₄, but it displays peculiar behavior. First, and unlike most other catalysts, it possesses broad scope with respect to the alkene. Thus, conjugated esters, nitriles, ketones, and aldehydes, including the notoriously problematic crotonaldehyde, undergo Heck reaction in generally good to excellent yields in the presence of Pd(OAc)₂ and CEPU. Second, it accepts only electron-rich aryl iodides in the arylation of the above substrates, but it performs well with either electron-rich or electron-deficient aryl halides in the arylation of simple acrylic systems. This paper expands the scope of our previous work by disclosing additional examples of Heck reactions promoted by the Pd(OAc)₂/CEPU system.

The original Liu–Guo catalyst [1:2 complex of Pd(OAc)₂ with *N*-phenylurea (NPU)]³ became of interest to us as a consequence of

very favorable results obtained in the arylation of protected (*S*)-vinylglycinol, leading to homotyrosinol derivatives.⁴ Thus, the Liu–Guo system outperformed even highly efficacious complexes of Pd with costly *S*-Phos.⁵ Such a positive experience provided an incentive to evaluate the catalytic ability of the Pd(OAc)₂/NPU system in other common Pd mediated coupling reactions. Liu and Guo had already established that their catalyst functions well in Suzuki processes;³ therefore, we focused our attention on Sonogashira⁶ and Negishi⁷ couplings. The Pd(OAc)₂/NPU system gave disappointing results in representative Sonogashira reactions, and since superior protocols are already available for such transformations, research in this area was quickly halted. The catalyst also performed poorly in Negishi reactions involving arylzinc halides. Unexpectedly, however, the attempted Negishi coupling of commercial alkylzinc agent **1** (Table 1) with methyl 4-iodobenzoate afforded cinnamic-type ester **2** in low yield (the balance of the aryl halide was recovered unchanged), while the same reaction with 4-iodoanisole produced mixtures of mono- and bis-aryl esters, **2** and **3**. A plausible mechanism for the formation of such products involves transmetalation of **1** to Pd(II), followed by β-hydrogen elimination. The resulting ethyl acrylate may then undergo Heck-type mono- and bis-arylation. These results captured our attention for three reasons. First, a need had recently arisen in our group for quantities of 3,3-diarylanilines,⁸ which could be prepared⁹ from compounds **3** by hydrogenation and Evans¹⁰ azidation.¹¹ Second, it seemed to us that an improved protocol for the arylation of acrylate

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Table 1
Attempted Negishi reaction of organozinc compound **1** with aryl halides

Entry	Ar	% Pd	Solv.	Time (h)	Yield:	
					2 ^a	3 ^a
a	4-C ₆ H ₄ COOMe	100	THF	5	—	—
b	4-C ₆ H ₄ COOMe	20	THF	5	21	—
c	4-C ₆ H ₄ COOMe	5	DMF	5	12	—
d	4-C ₆ H ₄ COOMe	5	THF	5	11	—
e	4-MeO-C ₆ H ₄	50	THF	5	—	—
f	4-MeO-C ₆ H ₄	20	THF	24	—	—
g	4-MeO-C ₆ H ₄	5	THF	5	7	—
h	4-MeO-C ₆ H ₄	1	THF	24	11	16
i	4-MeO-C ₆ H ₄	1	Toluene	16	5	—
j	4-MeO-C ₆ H ₄	0.1	THF	24	17	15

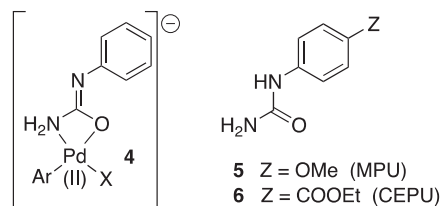
^a Yields of products purified by flash chromatography.

or cinnamate esters¹² under the influence of Pd(OAc)₂/NPU would be advantageous relative to earlier methods that require catalysts such as palladacycles,¹³ or Pd complexes incorporating highly electron-rich¹⁴ or polydentate¹⁵ phosphines (sometimes augmented by microwave irradiation),¹⁶ or supported Pd nanoparticles.¹⁷ Indeed, the Liu–Guo complex might well embody an alternative to an especially useful phosphine-free system described by Buchwald.¹⁸ Third, we were struck by the fact that the Pd(OAc)₂/NPU system performed best at low metal loading (0.1–5 mol %) and with electron-rich aryl halides. We thus launched an investigation of the Heck reaction of cinnamic and crotonic substrates in the presence of Pd(OAc)₂/NPU.

2. Results and discussion

As detailed previously,¹ test reactions with ethyl cinnamate and 4-iodoanisole revealed that the efficacy of Pd(OAc)₂/NPU was similar to that of the customary Pd(OAc)₂/PPh₃ system, although in either case the yields of Heck products were only moderate. However, the Liu–Guo complex exhibited broader substrate scope, promoting successful arylation of a range of cinnamic and crotonic systems, including notoriously troublesome crotonaldehyde. A solvent switch from DMF to NMP was beneficial, as confirmed in subsequent experiments. Electron deficient methyl 4-iodo-benzoate failed to undergo Heck coupling with ethyl cinnamate in the presence of Pd(OAc)₂/NPU (essentially quantitative recovery of unchanged substrates), even though it reacts efficiently with ethyl acrylate under the same conditions.

The influence of the electronic properties of the ligand on the performance of the catalyst was studied in an effort to improve the yields of the above reactions. Liu and Guo had found an inverse correlation between the pK_a of the N–H bond of various urea ligands and the catalytic activity of the corresponding complexes with Pd(OAc)₂ (the lower the pK_a, the higher the activity).³ They attributed the beneficial effect of phenylurea to the more facile accessibility of its anionic form and the ability the latter to ligate arylpalladium(II) species, leading to complexes of the type **4** (Scheme 1). On that basis, we surmised that further lowering of the pK_a of the N–H bond of the ligand might increase the catalytic efficiency of the resulting Pd complexes. To test this hypothesis, 4-(methoxy)phenylurea (**5**, MPU) and 4-(carboxy) phenylurea (**6**, CEPU) were examined as ligands in lieu of NPU, with the expectation that the more N–H acidic CEPU should perform much better than MPU. Relative to the original Liu–Guo system, the 1:2 complexes of Pd(OAc)₂ with CEPU or MPU



Scheme 1. Proposed structure of the NPU–Pd(II) complex **4** (Ref. 3) and structures of MPU (**5**) and CEPU (**6**).

both afforded much improved results in the Heck reaction of cinnamic and crotonic substrates with electron-rich aryl iodides. Whereas CEPU was definitely superior to MPU in our test arylation of ethyl cinnamate with 4-iodoanisole, and consequently our previous work¹ had focused exclusively on that catalyst, it ultimately transpired that the efficacy of the two systems is generally comparable, suggesting that factors other than purely electronic effects modulate the properties of phenylurea ligands. Results obtained in the arylation of various substrates with the representative electron-rich aryl iodides, *N,N*-dimethyl-4-iodoaniline, *N*-(*tert*-butoxycarbonyl)-4-iodoaniline, and 4-iodoanisole, are summarized in Table 2.¹⁹

Table 2

Comparison of the Pd–CEPU versus Pd–MPU catalysts in the arylation of cinnamic and crotonic substrates with electron-rich aryl iodides

Entry	R ¹	R ²	EWG	CEPU Yield ^a	E/Z ^b	MPU Yield ^a	E/Z ^b
a	Me ₂ N	Ph	COOEt	51	4.0:1	31	4.0:1
b		Me	COOMe	41	1.0:0	51	1.0:0
c		Me	CN	84	2.9:1	81	2.8:1
d		Me	CHO	71	5.3:1	79	5.4:1
e		Ph	CHO	98	2.3:1	98	5.7:1
f		Ph	COPh	99	2.0:1	77	2.0:1
g	BOCHN	Me	COOMe	51	1.0:0	55	1.0:0
h		Me	CN	99	2.7:1	95	2.6:1
i		Me	CHO	50	11.5:1	55	11.5:1
j		Ph	CHO	99	3.0:1	85	2.5:1
k		Ph	COOEt	71	3.0:1	77	3.0:1
l		Ph	COPh	77	3.0:1	83	3.0:1
m	MeO	Ph	COOEt	75	2.1:1	29	2.1:1
n		Me	COOMe	97	1.0:0	67	1.0:0
o		Me	CHO	76	3.0:1	54	3.2:1
p		Me	CN	92	3.5:1	83	3.4:1
q		Ph	CHO	84	2.6:1	99	2.6:1
r		Ph	COPh	66	2.2:1	53	2.3:1

^a Yield of products purified by flash chromatography.

^b Ratios measured by integration of ¹H NMR spectra.

Plain iodobenzene reacted to give the expected Heck products in moderate to good yields (Table 3). In all cases, ester, nitrile, ketone, and aldehyde substrates participated normally in the reaction. In particular, products arising from ‘reductive Heck’ processes²⁰ or homocoupling of the aryl halide (vide infra) were not apparent in the ¹H NMR spectra of crude reaction mixtures. By contrast,¹ aryl bromides reacted poorly, while aryl chlorides failed to react,²¹ as did, again, electron-deficient iodides (all recovered unchanged). As detailed previously, the arylation of substituted cinnamic esters proceeded in a satisfactory manner, as exemplified by compounds **10** (Scheme 2, 50–54% yield),¹ which are especially relevant to our need for 3,3-diarylalanines.¹

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