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α-Zinc *O*-Vinyl Carbamates as Anionic Friedel-Crafts Equivalents. Cross Coupling Reactions with Aryl and Heteroaryl Halides and Triflates

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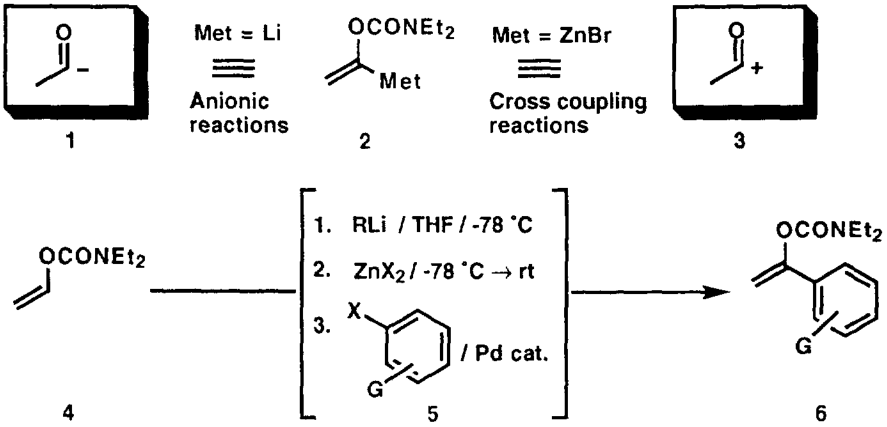
Abstract: A mild, efficient, and general Negishi cross coupling protocol, **4** + **5** → **6** is reported; the hydrolysis of products **6** to acetophenones demonstrates the anionic Friedel-Crafts equivalency of the overall synthetic operation.

In order to broaden the synthetic scope of α-lithio *O*-vinyl carbamates **2** (Met = Li), useful acyl anion equivalents **1** developed in our laboratories,[1] we have investigated and delineate herein the Pd-catalyzed cross coupling reaction of the corresponding α-zinc species **2** (Met = ZnBr) with aryl and heteroaryl halides and triflates which constitutes a general and efficient anionic alternative for Friedel-Crafts acylation **3**[2] (**Scheme 1**). The mild conditions and the compatibility with many functional groups, combined with the link to the directed *ortho* metalation protocol,[3] posits this methodology as an advantageous alternative to the classical electrophilic acylation process.[4]

Scheme 1



Salient results of the overall one-pot sequence, **4** → **6**, optimized by extensive variation of the X group and catalyst,[5] are summarized in Table 1. As expected, the efficacy of cross coupling followed the order I > OTf, Br while, surprisingly, the most common catalyst $Pd(PPh_3)_4$ for organozinc coupling[2] showed low reactivity especially for bromides and triflates in comparison to $PdCl_2(dppf)$.[6]

In order to determine the scope, a variety of substituted aryl iodides and bromides were tested with specific emphasis on establishing electronic effects of substituents and connections to *ortho* metalation. The results, depicted in Table 2, show that for coupling of 2-DMG substituted ArX **5** (entries 2-5), X = I give significantly better yields than the corresponding X = Br systems with, respectively, $Pd(PPh_3)_4$ and $PdCl_2(dppf)$ catalysts. For both systems, low yields using less readily available $PdCl_2(dppf)$ were generally observed, presumably due to steric effects of the phosphine ligand.[6] Furthermore, for 3- and 4-substituted systems, EWGs give better yields than EDGs (compare entries 8, 11 and 12 with 9, 10), although entry 6 and 7 are exceptions.

Table 1. α-Zinc *O*-Vinyl Carbamate - ArX Cross Coupling. Effect of X and Pd Catalyst

Catalyst	5 (G = H) yield, % (reaction time)		
	PhI	PhOTf	PhBr
$Pd(PPh_3)_4$	68 (18 h)	10 (90 h)	13 (48 h)
$PdCl_2(dppf)$	95 (2 h)	84 (2 h)	72 (18 h)

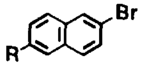
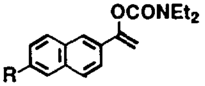
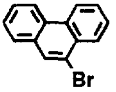
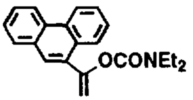
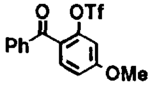
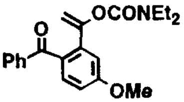
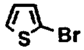
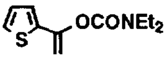
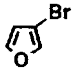
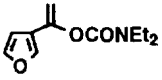
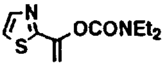
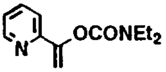
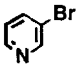
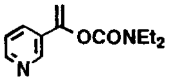
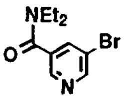
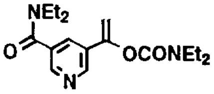
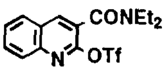
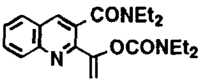
Table 2. α-Zinc *O*-Vinyl Carbamate - ArX (X = I, Br) Cross Coupling. ArX Variation

Entry	Product 6, G	yld,[a] % X = I[b]	Br[c]	Entry	Product 6, G	yld,[a] % X = Br[c]
1	2-Me		72	7	3-NO_2	31
2	2-Me	74	43	8	3-$CONEt_2$	76
3	2-OMOM	59	39	9	4-Me	52
4	2-$OCONEt_2$	65	38	10	4-OMe	30
5	2-$CONEt_2$	63[d]	[e]	11	4-NO_2	63
6	3-OMe		76	12	4-Cl	82

[a] Reported ylds correspond to chromatographed / distilled materials. [b] $Pd(PPh_3)_4$ cat. [c] $PdCl_2(dppf)$ cat. [d] Using $PdCl_2(dppf)$, a 34% yld was obtained. [e] Starting material was recovered.

Cross coupling of condensed aromatic and heteroaromatic bromides and triflates gives further scope to the methodology (**Table 3**). Thus naphthalene (entries 1-2) and phenanthrene (entry 3) substrates provide good yields of products as is the case of a benzophenone triflate (entry 4) which also illustrates the compatibility of ketone functionality in organozinc coupling[7] and suggests a potential solution to the steric problem associated with 2-substitution (**Table 2**). Coupling of heterocylic bromides[8] (entries 5-7, 10) were slow, and resulting in the isolation of considerable amounts of starting materials. Furthermore, the volatility of these products was high, causing difficulty in isolation. Bromopyridines[8] undergo smooth coupling (entries 8,9) while a quinoline triflate provides a modest result (entry 11).

Table 3. **α-Zinc *O*-Vinyl Carbamate - Condensed ArX and HetArX (X = Br, OTf) Cross Coupling. $PdCl_2(dppf)$ Catalyst**

Entry	ArX	Product	yld, [a] %
			
1	R = H	R = H	84
2	R = OMe	R = OMe	88 (71)[b]
3			81
4			84
5			31
6			19
7			31
8			87
9			64
10			21
11			40

[a] See footnote *a*, **Table 2**. [b] Using $Pd(PPh_3)_4$ catalyst.

In order to demonstrate the anionic Friedel-Crafts equivalency of **2**, the hydrolysis of a number of products (**Table 2**, entries 2-5) to the corresponding methyl ketones was effected.[9]

To conclude, we have developed an anionic Friedel-Crafts equivalent **1** which a) provides access to acylated aromatics and heteroaromatics, including *ortho* substituted products originating from DoM chemistry (**Table 2**, enries 3-5) and b) conveniently overrides normal electrophilic substitution rules in situations (entry 6, **Table 2**; entry 4, **Table 3**) where precursor iodides, bromides, or triflates are easily accessible.[10,11,12]

References and Footnotes

1. Sengupta, S. and Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680. Kocienski, P.; Dixon, N. J. *Synlett* **1989**, 52.
2. Pd(0)-catalyzed cross coupling of α-zinc ethyl *O*-vinyl ether with PhI constitutes the only previous example of the use of an ArX partner: Russell, C. E. and Hegedus, L.S. *J. Am. Chem. Soc.* **1983**, *105*, 943. Negishi E.-I.; Luo, F-T. *J. Org. Chem.* **1983**, *48*, 1560. For extensions, see DaSilva, A.; Snieckus, V. unpublished results.
3. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
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5. Others catalysts tested: PdCl$_2$(Ph$_3$)$_2$, PdCl$_2$(dppp), PdCl$_2$(dppf) + *n*-BuLi and DIBAH.
6. These results may be related to a faster transmetalation step in which the halide or triflate is displaced by the carbamate which, in turn may be a function of the wider P-Pd-P angle and longer P-Pd distance in the oxidative addition species involving PdCl$_2$(dppf), see Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T. and Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
7. Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349. Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F. Pietroni, B. *Synlett* **1990**, 47.
8. The unreactivity of 3-bromofuran and 3-bromopyridine with PhZnCl using Pd-catalysis has been reported: Negishi, E-I.; Luo, F-T.; Frisbee, R.; Matsushita, H. *Heterocycles* **1982**, *18*, 117.
9. Conditions: 2N HCl/MeOH/reflux/2-6 h gave the known methyl ketones in 85-90% yields.
10. *Representative Procedure*: To a stirred solution of *N,N'*-diethyl-*O*-vinylcarbamate (2.1 mmol) in anhydrous THF (10 mL) at -78 °C under nitrogen was added *s*-BuLi (2.3 mmol, 1.4 M in hexane). After 1 h, a solution of ZnBr$_2$ (2.5 mmol) in THF (5 mL) was added via syringe. The resulting mixture was stirred for 15 min and allowed to warm to rt. A solution of Pd catalyst (0.11 mmol) and bromobenzene (3.2 mmol) in THF (5 mL) was added and the reaction mixture was stirred at rt for 48 h. The reaction was quenched by satd NH$_4$Cl solution (10 mL), extracted with ether (20 mL x 3) and the combined organic extract was washed with water and brine solution, dried over MgSO$_4$, and evaporated *in vacuo*. Flash chromatography on silica gel (hexane/ethyl acetate as eluent) afforded pure products **6**.
11. All compounds show analytical and spectral (^{1}H, ^{13}C NMR, IR, MS) data consistent with the given structures.
12. We acknowledge NSERC Canada for support under the Research Grant and Monsanto Industrial Research Chair Programs. VS is grateful to Glaxo Wellcome for a Visiting Professorship at Duke and Professors M. Pirrung and N. Porter for warm hospitality. SS and NS gratefully acknowledge Universita di Pisa (Italy) and "Gobierno Vasco" (Spain) respectively for fellowships without which this work would not have been achieved. We thank Dr. B. P. McKibben for carrying out the experiment of entry 11, **Table 3**.

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