Pergamon

Tetrahedron Letters 39 (1998) 8807–8810

TETRAHEDRON LETTERS

Synthesis of Arylacetates by the Palladium-Catalyzed Cross-Coupling of Aryl Bromides and Copper(II) Enolates

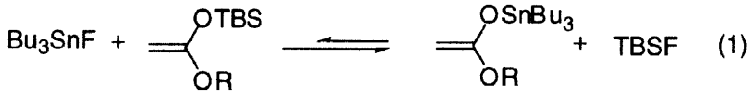
Fabio Agnelli and Gary A. Sulikowski*

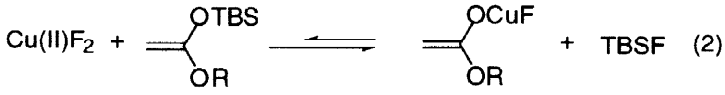
Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received 1 September 1998; revised 14 September 1998; accepted 15 September 1998

Abstract: Palladium-catalyzed cross coupling of aryl bromides and silylketene acetals in the presence of tributyltin fluoride or copper(II) fluoride is described.

A great deal of attention has been given to the synthesis of aryl acetates and propionates, mainly due to the analgesic and antiinflammatory properties demonstrated by this class of compounds.[1] One possible strategy for preparing arylacetates is the palladium-catalyzed reaction of aryl halides and ethoxy(trialkylstannyl)acetylenes to afford ethoxyethynylarenes, which on solvolysis give ethyl arylacetates.[2] A more direct approach to both acetates and propionates consists of the direct coupling of aryl halides and ester enolates, as in the case of nickel and palladium catalyzed cross-coupling of aryl halides with Reformatsky reagents or tin enolates.[3-6] A convenient synthesis developed by Musco and Santi involved the palladium-mediated coupling of trimethylsilylketene acetals with aryl triflates or halides in the presence of thallium acetate to provide alkyl 2-arylalkanoates in fair to good yields.[7] The main drawbacks of the current preparative methods include the use of toxic metals and variable chemical yields.





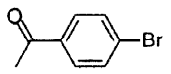
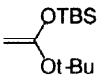
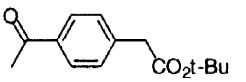
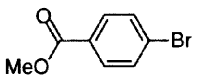
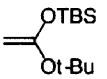
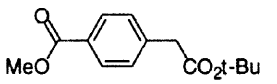
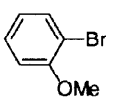
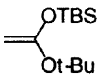
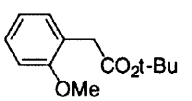
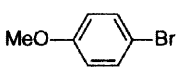
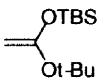
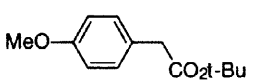
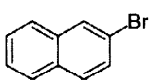
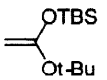
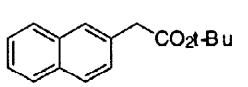
Kuwajima and Urabe reported that tin enolates, generated *in situ* from silyl enol ethers in the presence of tributyltin fluoride, undergo palladium catalyzed cross-coupling with aryl bromides to afford alpha aryl ketones.[8] As a logical extension of this work we examined the *in situ* generation of tin ester enolates starting from silylketene acetals (eqn 1) and their cross-coupling with aryl bromides by palladium catalysis.[9] Subsequently we recognized that copper enolates, analogously generated *in situ* from silylketene acetals and copper(II) fluoride (eqn. 2), could undergo the same type of reaction with the added benefit of the low toxicity of copper salts.[10]

Our investigations started with the use of tributyltin fluoride as the activating agent (cf. eqn 1). To this end, a mixture of aryl bromide, silylketene acetal,[11] tributyltin fluoride and $Pd(o\text{-}Tol_3P)_2Cl_2$ in refluxing benzene (Method A) afforded the corresponding t-butyl arylacetate in good yield (Table 1, entries 1-4). The

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01978-9

coupling proceeded smoothly with either electron withdrawing or releasing substituents on the aromatic ring, although a decrease in yield was observed in the case of ortho-bromoanisole (entry 3). A practical disadvantage of this method is that product isolation is often complicated by contaminating tin by-products.

Table 1. Coupling Reaction of Aryl Bromides and Silylketene acetal.

entry	Aryl Bromide	Silylketene Acetal	Product	Method[a]	Time (h)	Isolated Yield, %
1	 **1a**		 **2**	A B C	6 6 9	80 80 76
2	 **1b**		 **3**	A C	22 22	82 73
3	 **1c**		 **4**	A C	20 22	42 81
4	 **1d**		 **5**	A C	22 28	51 95
5	 **1e**		 **6**	C	16	75

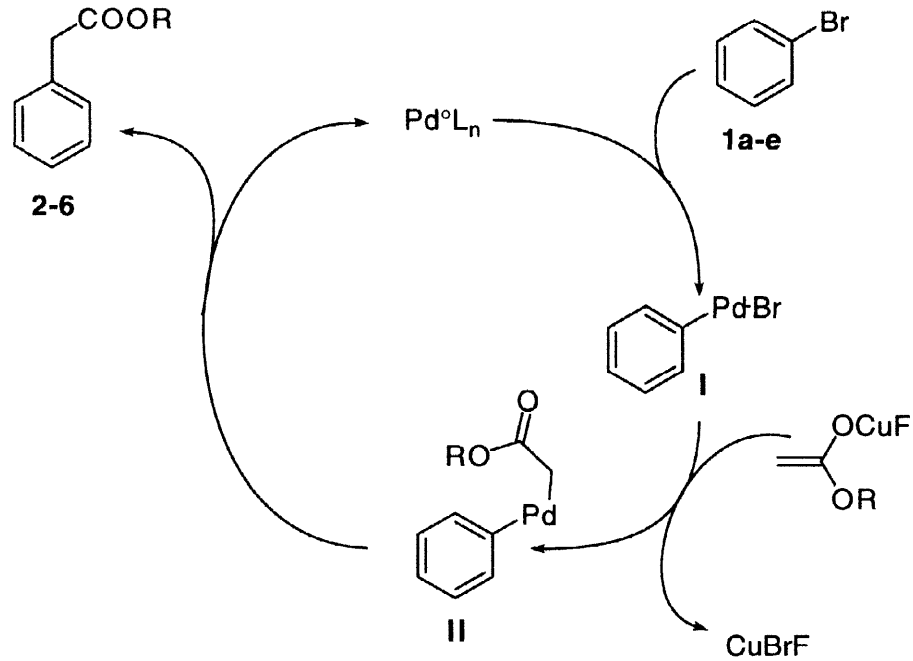
[a]Method A: 1 equiv of aryl bromide, 4 equiv of silylketene acetal, 2 equiv of Bu_3SnF, 2-5 mol % $Pd(Tol_3P)_2Cl_2$, benzene (0.25 M), reflux. Method B: 1 equiv of aryl bromide, 4 equiv of silylketene acetal, 2 equiv of CuF_2, 2-5 mol % $Pd(Tol_3P)_2Cl_2$, benzene (0.25 M), reflux. Method C: Same as method B, but tetrahydrofuran used in place of benzene.

A substantially simpler work-up procedure is possible when copper(II) fluoride is employed either in benzene (method B) or tetrahydrofuran (method C). In most cases the reaction proceeded with equal or improved yields using copper(II) fluoride as the activating reagent relative to method A, which uses tributyltin fluoride (Table 1, entry 3). A significant increase in yield was observed in cross-couplings with para- and ortho-bromoanisoles under these conditions (entries 3 and 4). Also, naphthyl acetate **6**, which was rendered inseparable from tin by-produts when using Method A, was easily purified by flash chromatography when using copper(II) fluoride as the activating agent (Method C).[12]

Control experiments show that the copper(II) fluoride-mediated reaction does not proceed in the absence of palladium catalyst and poorly (<10% product after 26 h) in the absence of copper(II) fluoride. These observations suggest a catalytic cycle starting with the oxidative addition of an aryl bromide (**1a-e**) to palladium(0) producing a palladium(II) intermediate **I** (Scheme 1). Subsequent transmetallation with the *in*

situ generated copper(II) enolate (**I** → **II**) leads to palladium(II) complex **II**. Reductive elimination from complex **II** provides the aryl acetate (**2-6**) and regenerates the palladium(0) catalyst.

Scheme 1



In conclusion, we have examined three sets of reaction conditions that effect the cross-coupling of the silylketene acetal derived from t-butyl acetate with a series of aryl bromides leading to the production of the corresponding aryl acetates. The most practical set of conditions consists of using two equivalents of copper(II) fluoride and bis-[tri(o-tolyl)phosphino] palladium(II) dichloride as catalyst in tetrahydrofuran.[13]

Acknowledgment. Support by the National Institutes of Health and the Welch Foundation (A-1230) is gratefully acknowledged. G. A. S. is an Alfred P. Sloan Fellow (1996-1998) and Eli Lilly Grantee (1996-1998). High-resolution mass spectra were obtained at the Texas A&M University Mass Spectrometry Service Center by Drs. Lloyd Sumner and Barbara P. Wolf on a VG Analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer. Funds to purchase the VG magnetic instrument came from National Science Foundation Grant CHE-8705697.

References and Notes

(1) Shen, T. Y. *Angew. Chem. Int. Ed. Eng.* **1972**, 11, 460.

(2) (**a**) Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Synlett* **1992**, 502. (**b**) Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1994**, *2*, 2032.

(3) (**a**) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273. (**b**) Orsini, F.; Pelizzoni, F.; Vallarino, L. M. *J. Organomet. Chem.* **1989**, *367*, 375.

(4) (**a**) Conan, A.; Sibille, S.; d'Incan, E.; Perichon, J. *J. Chem. Soc., Chem. Commun.* **1990**, 48. (**b**) Durandetti, M.; Nedelec, J.-Y.; Perichon, J. *J. Org. Chem.* **1996**, *61*, 1748.

(5) Kosugi, M.; Negishi, Y.; Kameyama, M.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3383.

(6) For the α-Arylation of ketone enolates, see: (**a**) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (**b**) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

(7) (**a**) Carfagana, C.; Musco, A.; Salles, G.; Santi, R.; Fiorani, T. *J. Org. Chem.* **1991**, *56*, 261. (**b**) Galarini, R.; Musco, A.; Pontellini, R.; Santi, R. *J. Mol. Cat.* **1992**, *72*, L11-L13. (**c**) Sakamoot, T.; Kondo, Y.; Masumoto, K.; Yamanaka, H. *J. Chem. Soc. Perk. Trans 1* **1994**, 235. (**d**) Sakamot, T.; Kondo, Y.; Masumoto, K.; Hiroshi, T. *Heterocycles* **1993**, *36*, 2509.

(8) (**a**) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831. (**b**) Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Sitoh, K.; Migita, T. *Chem. Lett.* **1982**, 939.

(9) Shibata, I.; Baba, A. *Org. Prep. and Proc.* **1994**, *26*, 87.

(10) (**a**) Kruger, J.; Carreria, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (**b**) Doherty, N. M.; Hoffman, N. W. *Chem. Rev.* **1991**, *91*, 553.

(11) Ita, Y.; Segawa, J.; Haruta, J.-i.; Yasuda, H.; Tamura, Y. *J. Chem. Soc., Perkins Trans. 1* **1982**, 1099.

(12) The coupling of p-bromoacetophenone with the silylketene acetal derived from tert-butyl propionate employing Method C provided the corresponding aryl propionate in only 28% yield.

(13) **Method C**: To a solution of *o*-bromoanisole **1c** (50 mg, 0.25 mmol), copper(II) fluoride (50 mg, 0.50 mmol) and bis-[tri(o-tolyl)phosphino] palladium(II) dichloride (6 mg, 3 mol%) in THF (1 mL) at 70°C was added silylketene acetal (287 mL, 1.0 mmol). The resulting mixture was stirred at this temperature for 9h, and then was allowed to cool to room temperature and was diluted with ethyl ether (4 mL). Saturated aqueous ammonium chloride (4 mL) was added and the biphasic mixture was stirred at room temperature for 30 min. The aqueous phase was extracted with ether (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient elution, 40:1 to 20:1 Hex/AcOEt) to give **4** (47 mg, 81%) as a colorless oil.