Pergamon

PII: S0040-4039(97)00644-8

Tetrahedron Letters, Vol. 38, No. 19, pp. 3455-3458, 1997

0040-4039/97 $17.00 + 0.00

Tandem Suzuki Cross-coupling-Heck Reactions

**Akihiko Kojima, Shinobu Honzawa, Christopher D.J. Boden,
and Masakatsu Shibasaki***

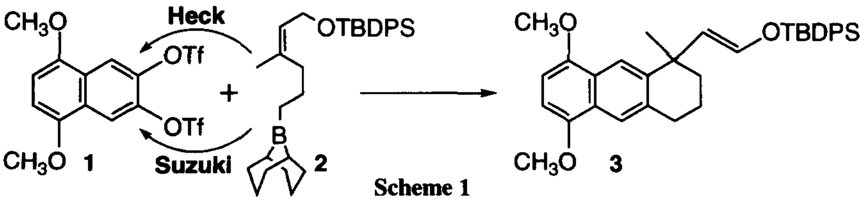
*Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan*

Abstract : Tandem Suzuki cross-coupling-Heck reactions were realized in satisfactory yields (up to 66%) by using triphenylarsine as a ligand or co-ligand.
© 1997 Elsevier Science Ltd.

Palladium-catalyzed coupling reactions have become one of the most versatile carbon-carbon bond-forming processes,[1] with both cascade[2] and asymmetric[3] variants having been developed in recent years.

In 1996 we reported a catalytic asymmetric total synthesis of biologically active halenaquinol which makes use of an asymmetric Heck reaction[3a] in a key step.[4] In that paper we reported the first example of a tandem Suzuki cross-coupling-asymmetric Heck reaction between a C_2-symmetric ditriflate **1** and a borane-olefin reagent **2** using BINAP as a chiral ligand to give **3** in 85% ee and 20% chemical yield, as shown in Scheme 1. This reaction is a novel variant on the theme of palladium catalyzed cascade (aka tandem, or "one-pot") reactions in that the cross-coupling step takes place before the Heck-type reaction,[2,5] and has the potential to become quite useful for carbon-frame construction. We thus decided to make a thorough study of this reaction, starting with an achiral system.

We now wish to report that by using triphenylarsine as a ligand, this type of tandem Suzuki-Heck reaction can be carried out so as to give a rather more satisfactory yield (up to 66%), and that furthermore another type of tandem Suzuki-Heck reaction between a borane-alkenyl triflate (generated *in situ* by hydroboration of compound **11**) and an alkenyl iodide **12** can be carried out in a chemo- and stereoselective manner using triphenylarsine as a co-ligand.



Scheme 1

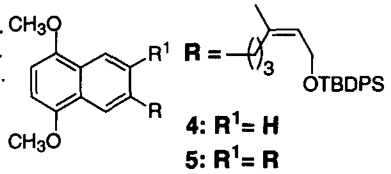
We screened a range of readily available ligands (triphenylphosphine, tri-2-furylphosphine,[6] tri-*o*-tolylphosphine,[7] triphenyl phosphite, triphenylarsine,[6] triphenylstibine, 1,1'-*bis*-(diphenylphosphino)ferrocene, ethylene-*bis*-diphenylarsine, *tert*-butyl isocyanide, 2,2'-bipyridyl), and were encouraged by the finding that the tandem product **3** could be obtained in 41% yield by using triphenylarsine. Although the **3** produced was of course racemic the yield obtained was comparable to the overall yield for stepwise synthesis of the product **3** (8 steps, 41% from 2,3-dihydroxy-5,8-dimethoxynaphthalene).[4] Tri-2-furylphosphine also gave a better result than BINAP, but the other ligands proved to be less effective giving in the main cross-coupling products such as **4** and **5**. These results seem to suggest that a "soft" ligand of monodentate donicity is appropriate for this tandem reaction. After optimization of the triphenylarsine-mediated reaction conditions (in respect of palladium source, base and solvent), the desired product **3** was obtained in 46% yield as shown in entry 7 (Table 1).

$$\mathbf{1} + \mathbf{2} \xrightarrow[\substack{6\text{ equiv }K_2CO_3\\ \text{THF, }60\text{ °C}}]{\text{Pd(0)-ligand}} \mathbf{3} + \mathbf{4} + \mathbf{5}$$

Table 1

entry	ligand	yield **3** (%)	**4** (%)	**5** (%)
1[a]	Ph_3P	-	-	-
2[a]	$(o\text{-tol})_3P$	trace	22	31
3[a]	$(2\text{-furyl})_3P$	27	13	-
4[a]	Ph_3As	41	25	-
5[b]	DPPF	trace	30	20
6[b]	$(Ph_2AsCH_2)_2$	trace	28	17
7[c]	Ph_3As	46	16	-

a : 20 mol% $Pd(OAc)_2$, 80 mol% ligand were used.
b : 20 mol% $Pd(OAc)_2$, 40 mol% ligand were used.
c : 10 mol% $Pd_2(dba)_3$, 80 mol% ligand were used.



4: R^1= H
5: R^1= R

By using these improved reaction conditions, the simpler ditriflate **6** was converted to the corresponding tandem product **9a** in 55% yield (Table 2, entry 1). Moreover, when using the disubstituted olefin-containing borane reagent **7** (entry 2)[8] the total yield of the tandem products was better (65%) than the yield when using a trisubstituted olefin, in spite of the fact that four products were obtained. Similarly, when using allylsilane **8**[8,9] as the borane reagent the tandem products were obtained in a total yield of 66%.

In other related work a Suzuki-Heck reaction between the borane-alkenyl triflate generated by *in situ* hydroboration of **11**[10] and the alkenyl iodide **12**[4] was successfully carried out using $PdCl_2(dppf)$ as catalyst, giving the tandem product **13** after suitable optimization of the reaction conditions (Table 3, entry1).

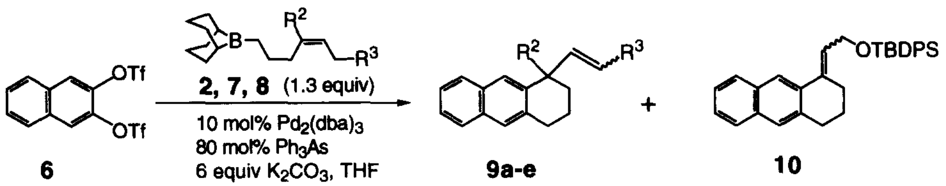


Table 2

entry	borane reagent	product: yield (%),	(total yield(%))
1	**2**: R^2= CH_3, R^3= OTBDPS	**9a**: 55, (*E*)- R^2= CH_3, R^3= OTBDPS	(55)
2	**7**: R^2= H, R^3= OTBDPS	**9b**: 10, (*E*)- R^2= H, R^3= OTBDPS	
		9c: 7, (*Z*)- R^2= H, R^3= OTBDPS	(65)
		10: 48[a]	
3	**8**: R^2= H, R^3= $Si(CH_3)_3$	**9d**: 50, R^2= R^3= H	(66)
		9e: 16, (*E*)- R^2= H, R^3= $Si(CH_3)_3$	

a: isomer ratio = 45:3. The stereochemistry has not been determined.

The use of triphenylarsine as co-ligand had a significant positive effect on this reaction, with the addition of an equimolar amount with respect to $PdCl_2$(dppf) increasing the yield of the tandem product to 65%. In contrast adding triphenylphosphine drastically *decreased* the yield, resulting in cross-coupling products such as **14** and **15** being obtained as the major products. It is interesting that the diastereoselectivity was complete[11] and that the intramolecular cross-coupling product **16** was not obtained.

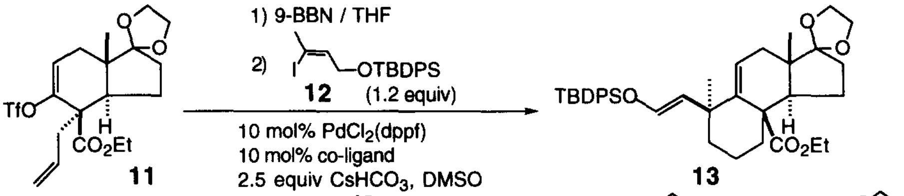
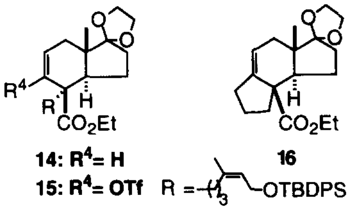


Table 3

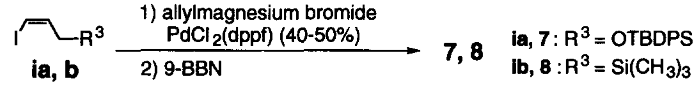
entry	co-ligand	yield **13**(%)	**14**(%)	**15**(%)
1	none	53	10	6
2	Ph_3P	4	24	37
3	Ph_3As	65	-	-



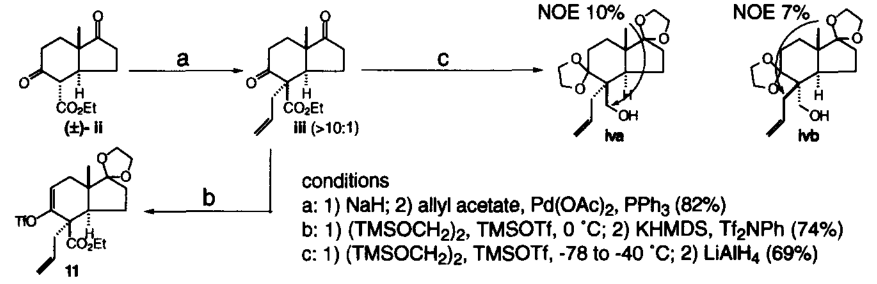
In conclusion, we have found that various types of tandem Suzuki-Heck reaction proceed in improved and rather more satisfactory yields when triphenylarsine is used as a ligand or co-ligand. It seems that this tandem reaction could become useful for carbon-frame construction.[12] Further studies of the **1**→**3** conversion with a view to its asymmetrisation are currently underway.

References and Notes

1. For a review of recent developments, see de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457 and references cited therein. For a comprehensive survey of synthetic organopalladium chemistry, see Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: New York, 1995.
2. For a review; see Grigg, R. *J. Heterocycl. Chem.* **1994**, *31*, 631. Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289.
3. (a) For asymmetric Heck reactions, see Shibasaki, M.; Sodeoka, M. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 956. Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6969. Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188. Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 6845. Tietze, L. F.; Schimpf, R. *Angew. Chem. Ed. Engl.* **1994**, *33*, 1089. Sakuraba, S.; Awano, K.; Achiwa, K. *Synlett* **1994**, 291. Moinet, C.; Fiaud, J.-C. *Tetrahedron Lett.* **1995**, *36*, 2051. (b) For other interesting asymmetric reactions using palladium complexes, see Hosokawa, T; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282 and references cited therein. Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101. For a review of allylic alkylations, see Trost, B. M.; Vranken, D. L. V. *Chem. Rev.* **1996**, *96*, 395.
4. Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 4876.
5. A palladium catalyzed one-pot process in which a carbonylation reaction was carried out prior to a Heck-type reaction was reported. See Tour, J. M.; Negishi, E.-I. *J. Am. Chem. Soc.* **1985**, *107*, 8289. Suzuki, T.;Uozumi, Y.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1593. Grigg, R; Putnikovic, B.; Urch, C. J. *Tetrahedron Lett.* **1996**, *37*, 695.
6. Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73 and references cited therein.
7. Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844. Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *ibid.* **1995**, *34*, 1848.
8. Compounds **7** and **8** were prepared from known **ia** and **ib**. Kabbara, J.; Hoffmann, C.; Schinzer, D. *Synthesis* **1995**, 299.

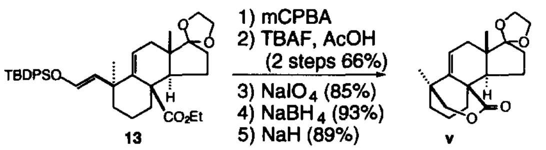


9. A useful intramolecular asymmetric Heck reaction using allylsilanes has been reported. See Tietze, L, F.; Raschke, T. *Liebigs Ann. Chem.* **1996**, 1981 and references cited therein.
10. Compound **11** was prepared from the known **ii** as follows, and the relative configuration of **11** was determined by examination of NOEs in the nmr spectra of **iva** and **ivb** , derived from **iii**. See Caselli, A. S.; Collins, D. J.; Stone, G. M. *Aust. J. Chem.* **1982** *35*, 799.



conditions
a: 1) NaH; 2) allyl acetate, Pd(OAc)$_2$, PPh$_3$ (82%)
b: 1) (TMSOCH$_2$)$_2$, TMSOTf, 0 °C; 2) KHMDS, Tf$_2$NPh (74%)
c: 1) (TMSOCH$_2$)$_2$, TMSOTf, -78 to -40 °C; 2) LiAlH$_4$ (69%)

11. The relative configuration of **13** was determined from the conversion of **13** to lactone **v** as follows.



12. Typical procedure: To a solution of the freshly distilled cross-coupling product derived from **ib** (20.1 mg, 0.13 mmol) in dry THF (0.283 mL), a freshly prepared 9-BBN solution in THF (from 9-BBN dimer (purchased from Aldrich Chemical Co., Inc.), and dry THF, then titrated)(0.46 M, 0.283 mL, 0.13 mmol) was added at 0 °C under Ar. After stirring at 23 °C for 12 h, the solution was added to a solution of **6** (42.4 mg, 0.10 mmol), K_2CO_3 (82.9 mg, 0.60 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (10.4 mg, 0.01 mmol), and Ph_3As (24.5 mg, 0.08 mmol) in dry THF (1.5 mL) under Ar. The mixture was degassed by freeze-pump-thaw cycles, stirred at 60 °C for 24 h. After cooling, the reaction mixture was diluted with AcOEt, washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane) to give a mixture of **9d** and **9e** (14.8 mg, **9d**:**9e** = 3.1:1, by ^{1}H-NMR).

(*Received in Japan* 13 *March* 1997; *revised* 31 *March* 1997; *accepted* 4 *April* 1997)