Palladium catalysed alkylative dimerization between pronucleophiles and vinyltins

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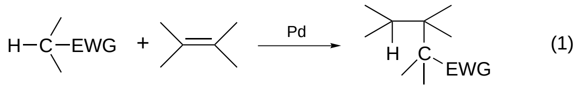
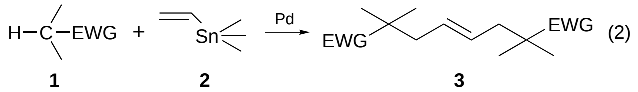
In the presence of catalytic amounts of $Pd_2(dba)_3$·$CHCl_3$ and dppb, the reaction of pronucleophiles 1 with vinyltins 2 gives the corresponding alkylative dimerization products of the vinyl group, 1,4-disubstituted butene derivatives 3, in good to high yields.

Palladium catalysed addition of carbon pronucleophiles to unactivated C–C double bonds is becoming an important new procedure for C–C bond formation[1–4] [eqn. (1)]. It has been



reported that allenes,[2] dienes[3] and enynes[4] can be used as the unactivated olefinic compounds for the pronucleophile addition.

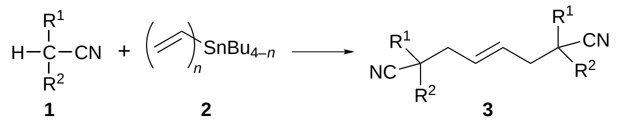
However, until now, it was not known that simple alkenes undergo this type of addition in the presence of palladium catalysts. During this investigation, we have found that the palladium catalysed reaction of vinyltins **2** with certain pronucleophiles **1** gives the corresponding alkylative dimerization products of the vinyl group, 1,4-disubstituted butene derivatives **3** [eqn. (2)].



The results are summarized in the Table 1. The reaction of ethyl 2-phenyl-2-cyanoacetate **1a** (1 equiv.) with vinyltributyltin **2a** (1 equiv.) in the presence of $Pd_2(dba)_3$·$CHCl_3$ (10 mol%) dppb (20 mol%) in THF at room temperature gave the alkylative dimerization product **3a** in 51% yield (entry 1). Very interestingly, the yield of **3a** increased to 81% using divinyldibutyltin **2b** instead of **2a** (entry 2). The reaction of **1a** (1 equiv.) with **2a** (2 equiv.) produced **3a** in 51% yield, indicating that the increase of the yield in the reaction with **2b** was not due to the presence of two vinyl groups in **2b**. The reaction of **1a** with tetravinyltin **2c** afforded **3a** in 78% yield (entry 3), pointing out that the presence of two vinyl groups in the reagent molecule is enough to enhance the chemical yield. The reaction of phenylmalononitrile **1b** with **2b** produced **3b** in 89% yield (entry 4). To investigate the influence of electronic effect of phenyl substituents upon the product yield, the *para*-substituted arylcyanoacetates **1c**, **1d** and **1e** were treated with **2b** and the corresponding alkylative dimerization products **3c**, **3d** and **3e** were obtained in 75, 71 and 65% yield, respectively (entries 5–7). Therefore, electronic effects did not exert a significant influence upon the product yield. The reaction of isopropylmalononitrile **1f** with **2b** gave **3f** in 43% (entry 8). The *trans* stereochemistry of the products **3** was determined unambiguously by comparison with authentic samples prepared independently.[5] No *cis*-isomers were detected in all reactions. Other pronucleophiles, such as malononitrile, diethyl malonate and diethyl phenylmalonate, did not react with vinyltins **2**. The alkylative dimerization took place with other catalysts such as $Pd(PPh_3)_4$ and $Pd(dba)_2$, but the use of $Pd_2(dba)_3$·$CHCl_3$ gave the best result. The reaction did not proceed at all with $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $Pt(PPh_3)_4$ as catalyst.

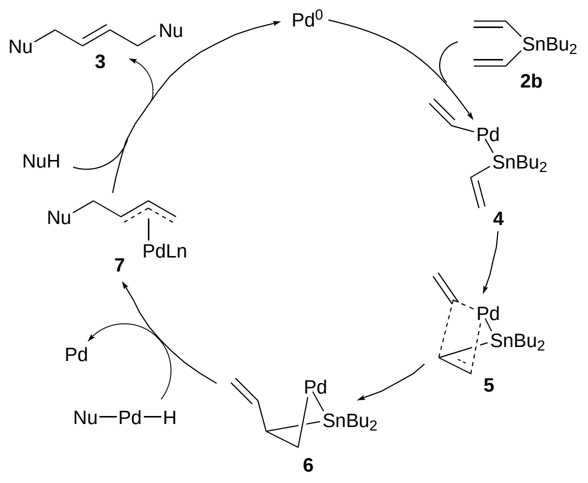
The reaction of **1a** with **2b** is representative. A mixture of $Pd_2(dba)_3$·$CHCl_3$ (51.7 mg, 0.05 mmol), dppb (42.6 mg, 0.1 mmol), ethyl 2-phenyl-2-cyanoacetate **1a** (0.09 ml, 0.52 mmol) and divinyldibutyltin **2b** (0.13 ml, 0.51 mmol) in dry THF (3 ml) was stirred under an argon atmosphere at room temperature for 2 days. The reaction was monitored by TLC analysis, and the

Table 1 Palladium catalysed alkylative dimerization of vinyltins[a]



Entry	Pronucleophile			Vinyltin		Product	Isolated yield (%)
		R¹	R²		*n*		
1	**1a**	Ph	CO_2Et	**2a**	1	**3a**	51
2	**1a**	Ph	CO_2Et	**2b**	2	**3a**	81
3	**1a**	Ph	CO_2Et	**2c**	4	**3a**	78
4	**1b**	Ph	CN	**2b**	2	**3b**	89
5	**1c**	*p*-$MeOC_6H_4$	CO_2Et	**2b**	2	**3c**	75
6	**1d**	*p*-ClC_6H_4	CO_2Et	**2b**	2	**3d**	71
7	**1e**	*p*-$CF_3C_6H_4$	CO_2Et	**2b**	2	**3e**	65
8	**1f**	Pr^i	CN	**2b**	2	**3f**	43

[a] The reaction of **1** (0.5 mmol) with **2** (0.5 mmol) was carried out in the presence of $Pd_2(dba)_3$·$CHCl_3$ (10 mol%) and dppb (20 mol%) in THF at room temperature.

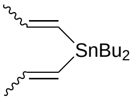


Scheme 1

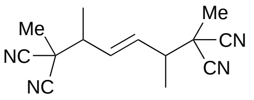
starting materials disappeared after 2 days. The reaction mixture was purified by silica gel flash column chromatography using hexane–ethyl acetate (10 : 1) as eluent, giving the alkylative dimerization product **3a** (88.5 mg, 0.21 mmol) in 81% yield.

A plausible mechanism for this unprecedented alkylative dimerization reaction is shown in Scheme 1, although it is speculative. The oxidative insertion of Pd^0 into the carbon–tin bond of **2b** would produce the vinylpalladium intermediate **4**. The intramolecular carbopalladation to the double bond of a vinyl group would afford the allyltin–palladium complex **6** *via* **5**. It is known that the palladium catalysed reaction of allyltin with certain pronucleophiles (NuH) gives the corresponding allylation product (CH_2=$CHCH_2$Nu).[6] Accordingly, it is probable that **6** would react with pronucleophiles to give the π-allylpalladium complex **7**. The Trost–Tsuji type reaction of **7** with pronucleophiles (NuH) would give the butene derivatives **3**.

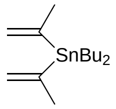
In order to gain an insight into the mechanism for the alkylative dimerization, the reaction of dibutyldiprop-1-enyltin **2d** with methylmalononitrile **1g** was carried out under similar conditions as above. The alkylative dimerization product **3g** was obtained as a mixture of diastereoisomers in only 10% yield; the ratio of the diastereomers was not determined. Furthermore, the reaction of dibutyldi(1-methylethenyl)tin **2e** with **1a** did not proceed at all and the starting materials were recovered. Perhaps the carbopalladation step becomes sluggish in the reaction of **2d** (the similar step for **2b** is shown in Scheme 1, from **4** to **6**) because of the steric effect of a β-methyl subsituent, and an α-methyl substituent would stop the carbopalladation step completely, as was observed in the reaction of **2e**. Dibutyldi(*cis*-oct-1-enyl)tin **2f**, which was synthesized in our laboratory by the method reported recently,[7] was treated with $Pd_2(dba)_3$·CHCl (10 mol%) and dppb (20 mol%) in dry THF at room temperature for 1 day, and *cis*,*cis*-hexadeca-7,9-diene **8** was obtained in 23% yield along with recovered **2f** [eqn. (3)]. This result clearly indicates that the oxidative insertion of Pd^0 into the carbon–tin bond of **2f** takes place readily, although it is not clear at present how the stereoselective dimerization of the *cis*-octenyl group proceeds under the reaction conditions.[8] Although the reaction of **8** with pronucleophiles was not investigated, the reaction of certain dienes, such as buta-1,3-diene and 2-methylbuta-1,3-diene, with pronucleophiles (**1a** and **1g**) under the same reaction conditions as above gave only mono-adducts in high yields:[9] no traces of the double addition products **3** were found. This result clearly indicated that the palladium catalysed reaction of vinyltins with pronucleophiles does not form dienes as intermediates.



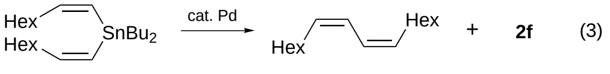
2d



3g

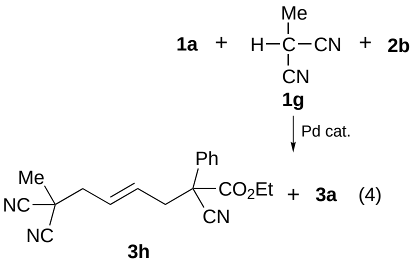


2e



23% 14%

Finally, the reaction of **2b** in the presence of two different kinds of pronucleophiles was carried out in order to ascertain whether a second pronucleophile (Nu'H) can participate at the stage from **7** to **3** [eqn. (4)]. A mixture of **1g** (0.5 mmol), **2b** (1.0 mmol), $Pd_2(dba)_3$·$CHCl_3$ (0.1 mmol) and dppb (0.2 mmol) in dry THF was stirred at room temperature for 30 min and then the second pronucleophile **1a** (0.5 mmol) was added. The mixture was stirred for 2 days. The cross-coupling product **3h** was obtained in 5% yield along with **3a** (50%). Since the reactivity of **1g** is lower than **1a**, the homo-coupling product **3a** was afforded as the major product. There is still room for improvement in order to produce a synthetically useful cross-coupling procedure, but the experimental results suggests that the process shown in **7**→**3** would intervene in the alkylative dimerization.



Although further investigation is needed to establish the mechanism for this unprecedented reaction, the coupling is useful for the synthesis of functionalized but-2-ene derivatives.

Footnotes and References

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