Enantioselective palladium-catalysed conjugate addition of arylsiloxanes†

Francesca Gini, Bart Hessen, Ben L. Feringa and Adriaan J. Minnaard*

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The complex formed from $Pd(CH_3CN)_4(BF_4)_2$ and (*R*,*R*)-MeDUPHOS is a highly enantioselective catalyst for the asymmetric conjugate addition of aryltriethylsiloxanes to a variety of unsaturated ketones, lactones and lactams.

The asymmetric transition-metal catalysed conjugate addition of organometallic reagents is of great importance for the formation of enantiopure β-substituted carbonyl compounds.[1] With respect to the addition of aryl and alkenyl groups, the rhodium-catalysed asymmetric addition of boronic acids pioneered by Hayashi and Miyaura[2] shows excellent enantioselectivities with a variety of ligands.[3] In studies based on earlier work of Miyaura *et al.*,[4] our group showed recently that the corresponding palladium-catalysed addition of arylboronic acids provides a versatile alternative.[5]

As an alternative to boronic acids,[6] organosilicon compounds have attracted much attention in recent years due to their low toxicity and high stability to both air and moisture. Especially aryltriethoxysilanes are low-cost and can be readily prepared nowadays in one step by a Barbier-type reaction of the corresponding aryl bromide and tetraethoxysilane at room temperature.[7] In contrast to arylboronic acids,[8] arylsiloxanes are easily purified by distillation or chromatography. Transmetalation, however, is considerably more difficult compared to arylboronic reagents, requiring highly efficient catalysts.

A number of examples of rhodium-catalysed enantioselective conjugate addition of aryl- and alkenylsilanes have been reported in the literature.[9] Both the groups of Miyaura and Denmark reported achiral palladium complexes that catalyse the conjugate addition of arylsiloxanes.[10] The enantioselective addition of aryltrifluorosilanes has been reported as well.[11] The corresponding enantioselective reaction using palladium(II) catalysts, however, has been elusive until now.

Herein we report the highly enantioselective conjugate addition of aryltriethoxysilanes using a Pd(II)–MeDUPHOS catalyst.

Initially, we studied the conjugate addition of phenyltriethylsiloxane **2a** to 2-cyclohexenone **1a** applying the conditions we developed earlier for the conjugate addition of arylboronic acids: 5 mol% of $Pd(CF_3COO)_2$ and 5.5 mol% of (*R*,*R*)-MeDUPHOS in dioxane–water (10 : 1) at 100 °C. After 24 h, 90% conversion of starting material **1a** into a mixture of cyclohexanone and phenol was observed, without any traces of conjugate addition product. To our delight, the use of $Pd(CH_3CN)_4(BF_4)_2$ instead afforded the desired 1,4-addition product **3a** in 94% ee although the isolated yield turned out to be only 30%. The corresponding Heck-type product was not formed at all but by GC analysis considerable amounts of cyclohexanone and phenol were detected again, besides **3a**. The palladium complex catalysed the disproportionation by reduction and oxidation of the starting material as shown by the outcome of the reaction carried out in the absence of $PhSi(OEt)_3$: 60% conversion into phenol and cyclohexanone was achieved after overnight reaction. The oxidation of **1a** to phenol using palladium complexes is well known,[12] but the reduction of α,β-unsaturated enones instead is rare.[13]

The carbon–silicon bond of arylsiloxanes is known to be very stable and this slows down the transmetalation step hence allowing the side reaction to occur.[14] Additives able to coordinate to Si can increase the reactivity of arylsiloxanes. Fluoride is well known to be an efficient activator. Among the fluoride sources tested the most efficient one proved to be ZnF_2.[15] The addition of 2 equivalent to the reaction in a dioxane–water mixture (10 : 1) at 100 °C gave full conversion in 2 h affording the desired product **3a** in 70% isolated yield and 97% ee. The efficiency of ZnF_2 compared to other fluoride sources might depend on its ability to act as a double activator: F^- increases the reactivity of the organosiloxane while Zn^{2+} coordinates to the oxygen of the carbonyl group, thereby increasing the reactivity of the enone. Despite this major improvement still around 10% of phenol and cyclohexanone were observed by GC analysis.

The role of water according to the proposed catalytic cycle[10a] is the hydrolysis of the Pd–C bond in the final step of the cycle leading to the formation of the conjugate addition product and regeneration of the active catalyst. A second role is the hydrolysis of the aryltrialkoxysilane to the arylsilanol which is considered to be the actual reagent.[9e] Variation of the reaction conditions led to the following observation. When the reaction was carried out at 100 °C with a lower dioxane : water ratio (4 : 1), full conversion to the conjugate addition product was achieved in 30 minutes with $< 5\%$ of side products and an excellent ee of 98%. In this reaction medium, even at a reaction temperature as low as 50 °C, and in the presence of only 1 equiv. of ZnF_2, the conjugate addition product was obtained with complete enantioselectivity ($> 99\%$) in 75% isolated yield, virtually without side products[16] (entry 1, Table 1). The catalyst loading could be decreased to 2 mol% affording the desired product in an overnight reaction without decrease in the ee. The use of 5 mol% (*R*,*R*)-MeBPE (Scheme 1) afforded comparable results but the conjugate addition product was obtained in 90% ee.

With these optimized conditions established, the scope of the reaction was examined (Table 1, Scheme 2). The steric hindrance of the arylsiloxane has an important influence on the reactivity,

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Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands. E-mail: A.J.Minnaard@rug.nl; Fax: +31 503634296; Tel: +31 503634258

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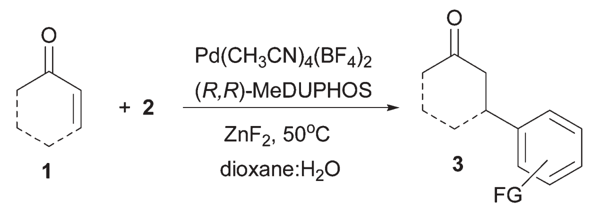
Table 1 The use of substituted arylsiloxanes in the addition to α,β-unsaturated compounds

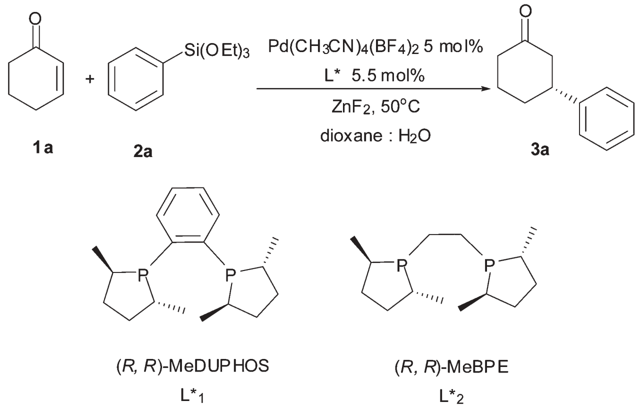


Entry[a]	Aryl siloxane	Substrate	Conv.[b] (%)	Yield[c] (%) (3)	ee[d] (%)
1[e]	**2a**	**1a**	100	75[f] (**3a**)	99 (*R*)
2[g]	**2b**	**1a**	15	nd (**3b**)	nd
3	**2c**	**1a**	100	60 (**3c**)	96 (+)
4[e]	**2d**	**1a**	100	64 (**3d**)	98 (*R*)
5	**2e**	**1a**	100	70 (**3e**)	95 (+)
6	**2f**	**1a**	100	70 (**3f**)	96 (+)
7	**2a**	**1b**	100	80 (**3g**)	90 (*R*)
8	**2a**	**1c**	100	84 (**3h**)	99 (*R*)
9	**2a**	**1d**	40	nd (**3i**)	90 (*S*)
10[g]	**2a**	**1d**	100	20 (**3i**)	88 (*S*)
11	**2a**	**1e**	100	40 (**3j**)	78 (+)
12	**2a**	**1f**	100	60 (**3k**)	94 (+)

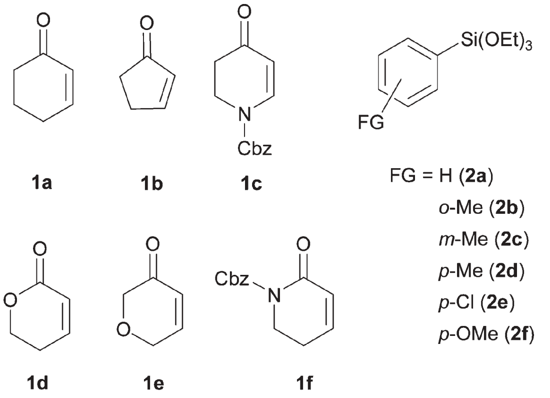
[a] Reaction conditions: $Pd(CH_3CN)_4(BF_4)_2$ (5 mol%), (*R*,*R*)-MeDUPHOS (5.5 mol%), dioxane : H_2O = 4 : 1, ZnF_2 (1 eq.), $ArSi(OEt)_3$ (2 eq.), 50 °C, 18 h. [b] By GC analysis with *n*-dodecane as internal standard or by TLC analysis. [c] After purification with column chromatography. [d] Determined by HPLC (see Experimental Section). [e] 5 h. [f] The yield of this reaction is lowered due to the volatility of the product. [g] 100 °C.

e.g. *o*-$MePhSi(OEt)_3$ afforded only 15% conversion even when the temperature was raised to 100 °C. The corresponding *m*- and *p*-tolylsiloxane gave full conversion with excellent enantioselectivities of 96% and 98% (entries 3 and 4).

Electron withdrawing groups on the arylsiloxane are tolerated and the reaction with *p*-$ClPhSi(OEt)_3$ afforded full conversion to the desired product in 95% ee (entry 5). This contrasts the result obtained in the conjugate addition of arylboronic acids,[5] where boronic acids with electron withdrawing groups gave incomplete conversion although with excellent enantioselectivity. Also an arylsiloxane bearing an electron donating group showed very good reactivity and enantioselectivity: the reaction with *p*-$MeOPhSi(OEt)_3$ afforded complete conversion into the 1,4-product in 96% ee (entry 6).[17]



Scheme 1



Scheme 2 α,β-unsaturated compounds and arylsiloxanes investigated.

Next, the scope of the reaction in terms of substrates was investigated. 2-Cyclopentenone afforded full conversion exclusively to the conjugate addition product with 90% ee. The reaction carried out with 2-cycloheptenone and 2*E*-octenone in contrast gave disappointing results: the main compound obtained with the reaction conditions optimized for **1a** was the corresponding saturated ketone. All attempts to increase the ratio toward the 1,4-addition product failed and acyclic substrates in general gave mainly conjugate reduction product.

Dihydropyridone **1c**, an important building block for alkaloid synthesis, showed excellent reactivity and afforded the 1,4-addition product with complete enantioselectivity (entry 8).[18] Lactone **1d** gave only 40% conversion when the reaction was carried out at 50 °C but increasing the temperature to 100 °C led to full conversion and the same high enantioselectivity (entries 9 and 10). Unfortunately, only 20% yield of **3i** was obtained.[19] Enone **1e**, prepared using RCM according to Hoveyda *et al.*,[20] gave full conversion to the desired product **3j** with 78% ee but only 40% isolated yield was obtained probably due to volatility of the product and instability of the starting material, as observed previously.

The enantioselective conjugate addition of alkyl and aryl nucleophiles to α,β-unsaturated lactams has not been studied extensively but leads to 4-substituted-2-piperidinones that are important synthons for natural products. The asymmetric addition of alkyl groups has been accomplished using dialkylzinc and trialkylaluminium reagents[21] whereas the complementary addition of aryl groups has been achieved using the Rh-catalysed addition of arylboronic acids.[22] We were very pleased to observe that the use of **1f** as a substrate in the reaction with $PhSi(OEt)_3$ gave full conversion overnight, affording the 1,4-addition product **3k** with an excellent 94% ee in 60% yield.

In conclusion, the first palladium-catalysed enantioselective conjugate addition of aryltrialkylsiloxanes is described. The catalyst, generated *in situ* from $Pd(CH_3CN)_4(BF_4)_2$ and (*R*,*R*)-MeDUPHOS, is efficient and excellent enantioselectivities are obtained for a series of substrates and aryltriethylsiloxanes. Aryltriethylsiloxanes are non-toxic, stable compounds, easy to handle and readily prepared or commercially available. The presented method could therefore be a versatile alternative to the corresponding rhodium- and palladium-catalysed addition of boronic acids.

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