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COMMUNICATION

Cavitand supported tetraphosphine: cyclodextrin offers a useful platform for Suzuki-Miyaura cross-coupling†‡§

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The cyclodextrin-tetraphosphine hybrid coined α-Cytep allows turnover numbers up to 340 000 000 000 and turnover frequencies up to 1 000 000 000 h^{-1} to be reached in Suzuki–Miyaura reactions. These exceptional figures are clearly linked to the outstanding longevity of the reactive species induced by the ligand α-Cytep and illustrates the rising potential of cyclodextrins in catalytic applications.

Since the original discovery and development of Pd-catalyzed coupling reactions that led to the recent chemistry Nobel Prize awarded to Heck, Suzuki and Negishi, a great deal of attention has been focused on the development of catalytic systems that would improve efficiency of the cross-coupling reactions. The practicality of the Suzuki-Miyaura reaction made it particularly popular in the pharmaceutical and chemical industries for which cost is a fundamental parameter.[1] The use of Herrmann-Beller palladacycles[2] or NHC-based ligands allows very high turn-over numbers (TONs) to be reached in Suzuki-Miyaura couplings,[3,4] and the search for catalytic systems allowing ultra-low loadings is still an ongoing field.[5] However, Buchwald's bulky monodentate dialkyl-biaryl phosphines are indubitably the current reference in terms of reactivity and efficiency,[6] the main reason for this increased reactivity of the monodentate bulky phosphine being the access to underligated reactive Pd species.[7] Disclosure of the tetradentate ligand **Tedicyp** by Doucet and Santelli[8] displaying exceptionally high TONs, was therefore a somewhat paradoxical breakthrough in this area. This discovery prompted the examination of various carbocyclic (cyclohexane,[9] cyclopentane,[8] cyclopropane[10]) or ferrocenyl-based[11] multiphosphines in low catalyst loading Suzuki-Miyaura couplings. Recently, Matt and Sémeril showed that cavity-shaped ligands could bring an added value in the efficiency of the Suzuki-Miyaura coupling.[12] Furthermore, although cavity-shaped tetraphosphines derived from calixarenes,[13] resorcinarenes[14] or cyclodextrins[15] (CDs) have been synthesized, none of them has been probed in a low-loading catalytic system to the best of our knowledge. In addition, we have shown that perbenzylated CDs regioselectively functionalized with two phosphines could serve as pseudo-enantiomeric platforms in enantioselective catalysis.[16] Furthermore, a benzylated CD platform would provide high steric hindrance that might prevent the agglomeration of Pd^0 into inactive species.[17] It was hence tempting and logical to study the potential of a CD-tetraphosphine hybrid in ultra-low loading catalysis. CD-appended multiphosphines are easy to synthesize, as first demonstrated by Matt and Armspach, who developed a tetraphosphine-CD called **α-TEPHOS** that was used to obtain tetra-metalated CDs.[15] However, we reasoned that hemilabile alkoxy groups remaining on the CD primary rim could be detrimental to efficiency due to parasital oxygen coordination. Accordingly, we designed the dideoxy-tetraphosphine α-cyclodextrine **α-Cytep** (Fig. 1).

α-Cytep was easily synthesized in 28% overall yield from native α-CD. An in-house perbenzylation/bis-debenzylation sequence afforded diol **1**,[18] which was dehydroxylated through LAH reduction of the corresponding dimesylate to afford compound **2**.[19] Regioselective acetolysis of the primary benzyloxy groups[20] to yield tetracetate **3** followed by deacetylation gave tetrol **4** in 76% yield. Subsequent mesylation afforded tetramesylate **5** which upon treatment with an excess of *in situ* formed lithium diphenylphosphide furnished **α-Cytep** in 61% yield. The tetraphosphine **α-Cytep** was protected and stored as its tetra borane complex **6** by simple treatment with BH_3·THF. The free ligand was regenerated using diethylamine right before its use in catalytic reactions. (Scheme 1)

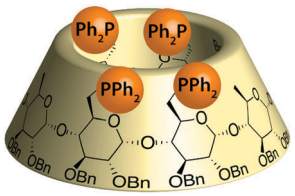

Fig. 1 Structure of **α-Cytep**.

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† In memory of David Gin, a great Glycoscientist.

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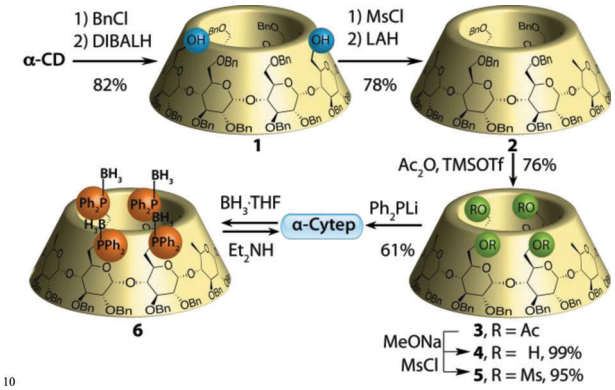
§ Electronic supplementary information (ESI) available: Experimental details of the synthesis of **α-Cytep**, spectroscopic analysis of the products, experimental details of the catalytic reaction. See DOI: 10.1039/c1cc12241j

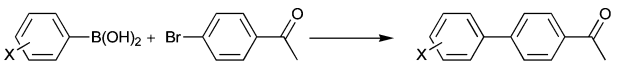


Scheme 1 Synthesis of **α-Cytep** from α-cyclodextrin (**α-CD**).

We then studied the **α-Cytep** catalyst's scope and limitations in Suzuki-Miyaura coupling at low loadings. We applied the same conditions as those reported for the **Tedicyp** tetraphosphine, using $[PdCl(\eta^3\text{-}C_3H_5)]_2$ as a palladium(0) precursor together with **α-Cytep**, in a 1 : 2 ratio but at a slightly lower (3×10^{-7}%) loading than the lowest used with **Tedicyp** (10^{-6}%),[8] and K_2CO_3 in refluxing xylenes for 7 days. Variation of the substitution pattern of the arylboronic acids did not induce any significant changes of reactivity, TONs remaining above 10^8, with TOF around 10^6 h^{-1} (Table 1). A survey of aryl halides showed more drastic reactivity changes (Table 2). As expected, electron-deficient aryl bromides gave better TONs ($>10^8$) than the electron-rich ones including the 4-MeO and 4-Me substituted aryl bromides, which were nevertheless still coupled with 6×10^7 and 10^8 TONs respectively.

Those results compare well with the best reported TONs (9.7×10^7) for Suzuki-Miyaura cross-coupling reactions obtained with **Tedicyp**[8] and Buchwald's phosphines.[6] However, this catalytic system is not as efficient as Buchwald's ligand for aryl chlorides. These observations suggest that these high TONs and TOFs are not due to a facilitated oxidative addition step, but as mentioned before, longevity of the catalyst can be the key to reaching high TONs.[21] We therefore monitored the progress of the reaction between phenylboronic acid and 4-bromoacetophenone over a 7-day period at 3×10^{-9}

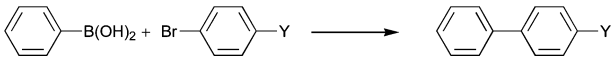
Table 1 Pd-catalysed cross-coupling variation of the boronic acids

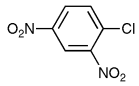


Entry[a]	X	Yield, %[b]	TOF, h^{-1}	TON
1	H	73%	1 400 000	240 000 000
2	4-F	58%	1 100 000	190 000 000
3	4-Cl	98%	2 000 000	330 000 000
4	4-BuO	47%	930 000	160 000 000
5	4-*t*Bu	41%	810 000	140 000 000
6	4-Me	46%	890 000	150 000 000
7	3-Me	79%	1 500 000	260 000 000
8	2-Me	38%	750 000	130 000 000

[a] The reactions were carried out in xylenes (0.25 M) at 120 °C under argon in presence of 4-AcC_6H_4Br (1 mmol), the appropriate $ArylB(OH)_2$ (2 mmol), K_2CO_3 (2 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$/**α-Cytep**: 1/2 (catalyst/substrate: 3×10^{-9}) for 7 days. [b] Determined by ^1H NMR analysis by using butadiene sulfone as external standard.

Table 2 Pd-catalysed cross-coupling variation of the aryl halides



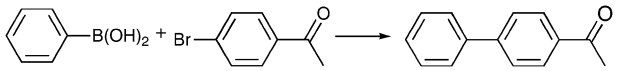
Entry[a]	Y	R	Yield, %[b]	TOF, h^{-1}	TON
1	MeCO	H	73 (70)[c]	1 400 000	240 000 000
2	MeO	H	19	380 000	60 000 000
3	Me	H	38	670 000	110 000 000
4	F_3C	H	40[c]	790 000	130 000 000
5[d]		H	10	950	160 000

[a] The reactions were carried out in xylenes (0.25 M) at 120 °C under argon in presence of the appropriate aryl-halide (1 mmol), phenylboronic acid (2 mmol), K_2CO_3 (2 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$/**α-Cytep**: 1/2 (catalyst/substrate: 3×10^{-9}) for 7 days. [b] Determined by ^1H NMR analysis by using butadiene sulfone as external standard. [c] Isolated yield. [d] Catalyst/Substrate = 10^{-6}.

catalyst/substrate ratio (entries 3–5, Table 3) and observed a steady increase of the yield with a constant 10^6 h^{-1} TOF indicative of a remarkable lasting of the catalyst. Those very encouraging results prompted us to further investigate this ability of our catalyst by lowering its loading to a 10^{-12} catalyst/substrate ratio, which led to vertiginous 340 000 000 000 TON and 1 000 000 000 h^{-1} TOF (entries 1–8, Table 3). As ligand-free Suzuki-Miyaura couplings have been also reported,[22] blank experiments were carried out. Predictably, no coupling product was observed in the absence of both palladium and **α-Cytep** (entry 9). When only **α-Cytep** was omitted, reaction occurred even at extremely low loadings (entries 10–12, Table 3). However, the presence of **α-Cytep** in the coupling process dramatically increases the observed TON when decreasing the loading (entry 12 *vs.* 5). Replacement of K_2CO_3 and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ by AcOK and $Pd(OAc)_2$ respectively did not improve the transformation (entries 14 and 15). As for **Tedicyp**, the ^{31}P NMR spectrum of the $[Pd(\eta^3\text{-}C_3H_5)(\text{α-Cytep})]^+$ BF_4^- complex synthesized using a known protocol[23] was recorded. It led to a similar observation: the presence of broad peaks exclusively around 25 ppm, indicative of phosphorous bound to the metal, in the 220–350 K temperature range, which also suggests a fast coordination–dissociation process of the four phosphines of the ligand.

In conclusion, we have synthesized and assessed a new CD-tetraphosphine hybrid coined **α-Cytep** which displayed exceptionally high TONs and TOFs in the Suzuki-Miyaura coupling. This property is clearly associated with its ability to super-stabilize the catalytic species over an exceptionally long period of time *via* multiple dynamic binding of the metal. We have hence shown that CDs can serve as interesting platforms for catalysis.[24] Indeed, a distinct feature of those platforms is their steric bulk and their relative flexibility allowing access to a wide variety of conformations, both of which contrast with the smaller rings studied so far in this area. It seems that our sugar-based platform is hence well suited to stabilize the catalytic species over time. In view of our results, other cavitand-based tetraphosphines should now be tested in low-loading catalysis.

Table 3 Pd-catalysed cross-coupling variation of catalyst loading



Entry	Ligand	c/s	Conversion[d] (yield),[e] %	t, d	TOF, h^{-1}	TON
1[a]	α-Cytep	10^{-3}	100	1	6	1000
2[a]	α-Cytep	10^{-6}	64	2	3800	640 000
3[a]	α-Cytep	3×10^{-9}	22 (22)	2.5	1 200 000	73 000 000
4[a]	α-Cytep	3×10^{-9}	35 (34)	4	1 200 000	110 000 000
5[a]	α-Cytep	3×10^{-9}	84 (73)[f]	7	1 400 000	240 000 000
6[a]	α-Cytep	3×10^{-10}	61 (59)	7	12 000 000	2 000 000 000
7[a]	α-Cytep	10^{-10}	78 (59)	10	25 000 000	5 900 000 000
8[a]	α-Cytep	10^{-12}	34 (34)	14	1 000 000 000	340 000 000 000
9	No Pd	—	0	14	—	—
10	—	10^{-3}	100	1	6	1000
11	—	10^{-6}	53	2	3000	530 000
12	—	3×10^{-9}	27 (21)	7	420 000	70 000 000
13	—	3×10^{-10}	Traces	7	—	—
14[b]	α-Cytep	3×10^{-9}	19 (17)	7	370 000	60 000 000
15[c]	α-Cytep	3×10^{-9}	65 (63)	7	1 250 000	210 000 000

[a] The reactions were carried out, at least twice, in xylenes (0.25 M) at 120 °C under argon in the presence of 4-AcC_6H_4Br (1 mmol), $PhB(OH)_2$ (2 mmol), K_2CO_3 (2 mmol) and the appropriate amount of $[PdCl(\eta^3\text{-}C_3H_5)]_2$/ **α-Cytep**: 1/2. See supporting information for details.§ [b] The reaction was performed with AcOK as base. [c] The reaction was performed with $[Pd(OAc)_2]$ as pre-catalyst. [d] Determined by ^1H NMR analysis of reaction mixture samples, based on bromoacetophenone. [e] Determined by ^1H NMR analysis by using butadiene sulfone as external standard. [f] Isolated yield: 70%.

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