DOI: 10.1002/adsc.200505283

Heterogeneous Palladium Catalysts Applied to the Synthesis of 2- and 2,3-Functionalised Indoles

Laurent Djakovitch,[a,*] Véronique Dufaud,[b] Rabah Zaidi[a]

[a] Institut de Recherches sur la Catalyse, UPR-CNRS 5401, 2 Avenue Albert Einstein, 69626 Villeurbanne, France
Phone: (+33)-472-44-53-81, Fax: (+33)-472-44-53-99, e-mail: laurent.djakovitch@catalyse.cnrs.fr
[b] Laboratoire de Chimie, UMR 5182, Ecole Normale Supérieure de Lyon, 46 Allée d'Italie, 69364 Lyon Cedex 07, France

Received: July 20, 2005; Accepted: January 31, 2006

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Heterogeneous palladium catalysts ($[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15) were applied to the synthesis of 2-functionalised indoles, giving generally high conversions and selectivities (>89% yield) using only 1 mol % [Pd]-catalyst under standard reaction conditions (polar solvent, 80 °C). For the synthesis of 2,3-functionalised indoles by cross-coupling arylation, the [Pd]/SBA-15 catalyst was found to be particularly interesting, producing the expected compound with =35% yield after 12 days of reaction, which is comparable to the homogeneous catalyst, $Pd(OAc)_2$ (=48% yield). In the course of the study, the dual reactivity of the indole nucleus was demonstrated: aryl bromides gave clean C–C coupling while aryl iodides led to a clean C–N coupling.

Keywords: C–N coupling reactions; cross-coupling arylation; heterogeneous palladium catalysts; immobilisation; indole synthesis; one-pot synthesis,

Introduction

The indole nucleus is an important substructure found in numerous natural or synthetic alkaloids.[1,2] The diversity of the structures encountered, as well as their biological and pharmaceutical relevance, have motivated research aimed at the development of new economical, efficient and selective synthetic strategies, particularly for the synthesis of functionalised indole rings.[3,4] Several classical methods have been reported, including the Fischer indole synthesis from arylhydrazones,[5,6] the Batcho–Limgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals,[7] the Gassman synthesis from *N*-haloanilines,[8,9] the Madelung cyclisation of *N*-acyl-*o*-toluidines[10–12] and the reductive cyclization of *o*-nitrobenzyl ketones.[3] While these procedures have contributed to this important area, some remain limited when the synthesis of functionalised indoles is required. Recently, transition-metal-catalysed transformations, and particularly palladium-catalysed reactions (Figure 1), have been developed, providing increased tolerance towards functional groups, and leading generally to higher reaction yields.[13,14] These methods include the palladium-induced cycloadditions of 2-haloanilines with terminal or internal alkynes (route 1, retrosynthetic disconnections a & e),[15–18] and the intra- or intermolecular reactions of 2-alkynylanilides with aryl or alkyl halides to give either 2-, or 2,3-functionalised indoles (route 4, disconnections b & e).[19–22] Other approaches are based on Heck-type cyclization reactions (route 2, disconnection a),[23,24] on reactions of alkynes with imines (route 5, disconnection c)[25] or on heteroannulation sequences achieved through palladium-catalysed arylamination reactions (disconnection f, not represented).[26–29] Some of these methods have proven to be most powerful and are currently applied in the target- or the diversity-oriented synthesis of indoles. Recently, a new disconnection pathway based on the intramolecular cyclisation of *N*-alkynyl-2-haloanilides followed by a C–N coupling reaction with primary or secondary amines has been reported by Witulski et al. (route 3, disconnection a & d).[30]

Another commonly used procedure for the synthesis of 2-functionalised indole rings was from 2-iodoaniline and alkynes.[31–33] This procedure usually requires two steps: the introduction of the ethynyl group onto the benzene ring, usually known as a Sonogashira C–C coupling reaction, followed by a heteroannulation, both of which are efficiently catalysed by Pd species. This procedure appeared particularly convenient for the synthesis of richly functionalised indoles regarding the high tolerance of the Sonogashira reaction and the heteroannulation step towards functional groups present in the substrates, arguments that probably contributed to its strong development using homogeneous catalysts. Furthermore, it was found to be efficient for the solid-phase synthesis of the indole nucleus,[34–36] a strategy generally applied for the generation of indole-based combinatorial libraries.

However, all of these methods rely on the use of soluble palladium catalysts, and only very few reports concern the use of heterogeneous catalytic systems, and almost none concern the use of heterogeneous palladium catalysts.

Indeed, heterogeneous catalysts present several important potential advantages over homogeneous catalysts including easy handling, easy separation of the catalytic species from the reaction mixture, which leads to the added advantage of catalyst recycling.[37–40] These features lead to a lower cost synthetic process for fine chemicals and to a greener synthesis. Thus, a great deal of effort has been devoted to the creation of recoverable catalysts which mimic the high selectivity of the homogeneous systems. A typical approach is to immobilise a homogeneous catalyst with well known catalytic properties onto a solid support with high inorganic surface area which offers the possibility of generating a great number of active sites. Mesostructured porous silicas (e.g., MCM-41, MCM-48, SBA-15) are attractive materials and attracted our attention as catalytic supports due to their specific surface area (which can reach 1000 m^2/g) and the possibility of tuning the pore size between 2–10 nm, properties which are also accompanied by very high thermal and mechanical stability.

In this contribution, we described the applicability of two heterogeneous palladium catalysts, one microporous, $[\mathrm{Pd(NH_3)_4}]^{2+}$/NaY, the other mesoporous, [Pd]/SBA-15, to the one-pot synthesis of 2-functionalised indoles and the first results concerning the arylation at the 3 position by a cross-coupling reaction.

Results and Discussion

Catalysts

The heterogeneous catalysts were prepared according to procedures already reported in the literature. The $[\mathrm{Pd(NH_3)_4}]^{2+}$/NaY (4.8% wt Pd) material was obtained simply by ion exchange of NaY zeolite using a 0.1 M aqueous solution of $[\mathrm{Pd(NH_3)_4}]^{2+}\ 2\ \mathrm{Cl}^-$.[41] The [Pd]/SBA-15 catalyst (2.1% wt Pd) was made by grafting the $[\mathrm{PdCl_2\{PPh_2\text{-}(CH_2)_2\text{-}SiCH_3(OCH_2CH_3)_2\}_2}]$ complex *via* the condensation of ligand alkoxide moieties with surface silanols inside the pores of a calcined SBA-15 mesoporous silica.[42] The hexagonal ordering of the palladium-functionalised material was confirmed by X-ray diffractometry and the integrity of the molecular metal precursor, in particular the phosphine ligand arrangement at the palladium atom, was indicated by CP-MAS ^{31}P NMR which exhibits the two resonances of *trans*- and *cis*-isomers of the grafted complex (see Supporting Information) as well as by elemental analysis (molar ratio P/Pd around 2).

Heterogeneous $[\mathrm{Pd(NH_3)_4}]^{2+}$/NaY and [Pd]/SBA-15 catalysts were then evaluated and compared to homogeneous catalysts, $\mathrm{Pd(OAc)_2}$ and the "palladacycle" $\{\mathrm{Pd[P(}o\mathrm{\text{-}C_6H_4CH_3)_2\text{-}(}o\mathrm{\text{-}C_6H_4CH_2)(CH_3CO_2)]}\}_2$, for the one-pot synthesis of 2- or 2,3-functionalised indoles.

Reactivity

As a part of our development of heterogeneously catalysed Sonogashira cross-coupling reactions, we described the synthesis of 2-phenylindole (**3**) from 2-iodoaniline and phenylacetylene catalysed by a $[\mathrm{Pd(NH_3)_4}]^{2+}$/$\mathrm{(NH_4)Y}$ species in good yields.[43] However, this example was rather limited and did not focus on the real potential

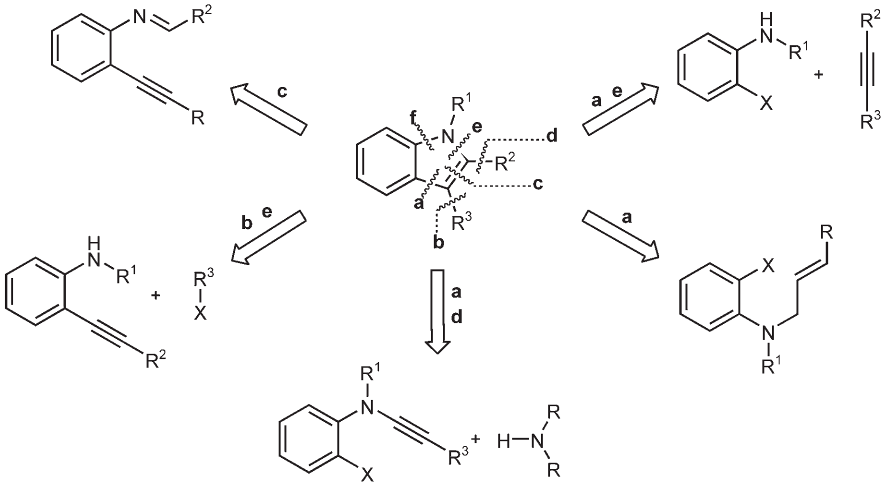
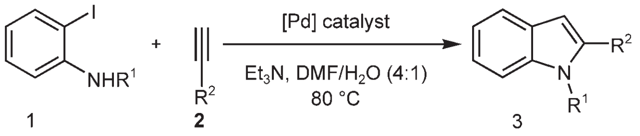


Figure 1. Retro-synthetic approaches toward the synthesis of indole nucleus catalysed by palladium.

of heterogeneous catalysts for the synthesis of fine chemicals. Therefore, we were interested in applying this method to the synthesis of other indole nuclei, particularly those having an alkyl group at the 2-position of the ring, such as fluvastatin,[44] as this substructure has been linked to the bioactivity of several molecules. With this objective, we initiated a project exploring the applicability of heterogeneous palladium catalysts based on micro-(NaY) as well as ordered mesoporous supports (SBA-15) with the aim of synthesising 2- and 2,3-functionalised indoles.

Initially, we examined the catalytic activity of the Pd catalysts for the synthesis of 2-functionalised indoles starting from 2-iodoaniline or, alternatively, N-tosyl-2-iodoaniline and a variety of terminal alkynes (Scheme 1). The heterogeneous $[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15 catalysts were compared to classical homogeneous catalysts [i.e., $Pd(OAc)_2$, Herrmann's "palladacycle"]. The same reaction conditions {5 mmol aryl halide, 7 mmol alkyne, 1 mol % [Pd], 10 mL DMF/H_2O (4:1), 80 °C} were applied for all substrates. The results are reported in Table 1.



R^1 = H or Ts

R^2 = Ph, n-Bu, $(CH_2)_3CO_2CH_3$, $C(CH_3)_2OH$

Scheme 1. Palladium-catalysed one-pot synthesis of 2-functionalised indoles.

In all cases, high conversions and high selectivities are observed, with isolated yields up to 76%. It was found that reactivity of 2-iodoaniline is higher than that of N-tosyl-2-iodoaniline, which was not expected given previous reports in the literature.[1,3] For example, for the reaction with phenylacetylene the full conversion of N-tosyl-2-iodoaniline requires up to 6 days, while that of 2-iodoaniline takes generally only 1 day. The contrast is much higher when using the 2-methylbut-3-yn-2-ol as the alkyne. These results contrast strongly with those generally reported in the literature for which the modification of the amino substituent on the aromatic substrate to an N-tosyl or an N-acetyl derivative leads to higher conversion. This observation is often related to higher rate of the heteroannulation step that is catalysed

Table 1. Palladium-catalysed, one-pot synthesis of 2-functionalised indoles (Scheme 1).

Product	R^1	R^2	Catalyst	Time [days]	Conversion [%][a]	GC Yield [%][a]
3a	H	Ph	$Pd(OAc)_2$	2	89	75
			Palladacycle[b]	3	100	30
			$[Pd(NH_3)_4]$/NaY	0.4	93	91
			[Pd]/SBA-15	0.1	100	95 (72)
3b	Ts		$Pd(OAc)_2$	2	100	76 (42)
			Palladacycle[b]	3	100	45
			$[Pd(NH_3)_4]$/NaY	6	100	91 (76)
			[Pd]/SBA-15	6	100	89 (65)
3c	H	n-Bu	$Pd(OAc)_2$	2	100	93 (55)
			$[Pd(NH_3)_4]$/NaY	1	100	89 (70)
			[Pd]/SBA-15	1	100	93 (62)
3d	Ts		$Pd(OAc)_2$[b]	4	100	52 (47)
			$[Pd(NH_3)_4]$/NaY	1	100	92 (52)
			[Pd]/SBA-15	1	100	93 (48)
3e	H	$C(CH_3)_2OH$	$Pd(OAc)_2$[b]	2	100	78
			$[Pd(NH_3)_4]$/NaY	1	100	94 (64)
			[Pd]/SBA-15	1	100	93
3f	Ts		$Pd(OAc)_2$	7	40	35
			$[Pd(NH_3)_4]$/NaY	8	80	74 (56)
			[Pd]/SBA-15	7	100	91 (67)
3g	H	$(CH_2)_3CO_2CH_3$	$Pd(OAc)_2$[b]	2	100	80
			$[Pd(NH_3)_4]$/NaY	1	100	91 (51)
			[Pd]/SBA-15	1	100	89
3h	Ts		$Pd(OAc)_2$	3	82	76
			$[Pd(NH_3)_4]$/NaY	1	100	91
			[Pd]/SBA-15	1	100	90 (61)

Reaction conditions: 5 mmol aryl halide, 7 mmol alkyne, 8 mmol Et_3N, 1 mol % [Pd] catalyst, 10 mL DMF/H_2O (4:1), 80 °C.

[a] Conversions based on unreacted aryl halide and yields were determined by GC with an internal standard (diethylene glycol di-n-butyl ether) ($\Delta_{rel} = \pm 5\%$). Values in parentheses correspond to isolated product yields.

[b] The mass balance between conversions and yields is related to the relatively high formation of aniline in these reactions.

by Pd(II) complexes.[13,14] From our results, it seems that such a conclusion is not applicable when heterogeneous catalysts are involved. This behaviour could be related to a change in mechanism or, more likely, to the different nature of the active palladium species that catalyses the heteroannulation, which implies different transition states.

Curiously, under our reaction conditions, the homogeneous $Pd(OAc)_2$ and the "palladacycle" show lower activities than the heterogeneous catalysts. We attributed this observation to a lack of stability of the homogeneous complexes. Alone, these results justify the development of heterogeneous catalysts in which the active palladium centres are well dispersed and isolated preventing thus a deactivation by sintering or palladium agglomeration.

At this stage, it was interesting to compare the initial activities of heterogeneous catalysts. This was done through the synthesis of 2-phenylindole under standard reaction conditions {5 mmol 2-iodoaniline, 7 mmol phenylacetylene, 1 mol % [Pd], 10 mL DMF/H_2O (4:1), 80 °C, 6 h, Figure 2}. As depicted in Figure 2a, when using the $[Pd(NH_3)_4]^{2+}$/NaY catalyst, an induction period of about 7 min is observed before the reaction starts. This period is probably due to the delay required to generate in the bulk solution the catalytically active Pd species through a dissolution process (see "Recycling and Leaching" below). After this period, an apparent "initial activity" of 18.4 mmol/$g_{Pd}\cdot$min is observed for the $[Pd(NH_3)_4]^{2+}$/NaY catalyst, somewhat less than that of 43.1 mmol/$g_{Pd}\cdot$min observed for the mesoporous based [Pd]/SBA-15 catalyst (Figure 2b).

Interestingly, for the [Pd]/SBA-15 catalyst no induction period was observed, indicating that the grafted Pd complexes are probably the active species, or efficient precursors, that are easily accessible to the reagents due to the larger pore aperture of the mesoporous supports (54 Å *versus* 7 Å for the NaY).

Generally, the reaction of less hindered alkynes, namely the hex-1-yne and methyl hex-5-ynoate, required shorter reaction times than with phenylacetylene when using heterogeneous catalysts, which was expected concerning the microporous nature of the zeolite supports (i.e., less limitation of the diffusion of the smaller substrate molecules).

Recycling and Leaching

After demonstrating the applicability of heterogeneous palladium catalysts ($[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15) for the synthesis of various 2-functionalised indoles, the questions regarding the recyclability and the leaching of active Pd species in solution for these heterogeneous catalysts were addressed.

The recycling was examined for the coupling reaction of 2-iodoaniline and phenylacetylene under optimised reaction conditions {5 mmol 2-iodoaniline, 7 mmol phenylacetylene, 1 mol % [Pd], 10 mL DMF/H_2O (4:1), 80 °C} over 6 h. The method used corresponds to the following procedure: after the first run of the catalyst, the reaction mixture was allowed to cool to room temperature and the catalyst was separated by centrifugation and washed twice with DMF/H_2O (4:1) and allowed to "dry" at room temperature for 12 h. The recycled palladium catalyst was then used without any regeneration as the fresh catalyst under the same reaction conditions. The procedure was repeated up to 5 recycles and the results obtained for the $[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15 are reported in Table 2. The apparent loss of activity could have several sources, including mechanical mass loss during the recycling protocol (centrifuge, decantation) or real catalytic site deactivation. Nevertheless, the activity of the recycled catalysts remained reasonable over the 2nd and 3rd runs before dramatically decreasing for the $[Pd(NH_3)_4]^{2+}$/NaY while that of the [Pd]/SBA-15 catalyst led to good conversions up to the 5th run showing definitively a better behaviour for potential applications in the fine chemical industry. Interestingly, the AAS analyses realised on the liquid phase at the end of each run showed < 0.5 ppm palladium. More rigorous attempts to detect catalytically active palladium were performed in an independent series of experiments (*vide infra*).

Leaching was examined for the coupling reaction of 2-iodoaniline and phenylacetylene under optimised reaction conditions using the hot filtration method: a catalytic run was started as for a standard reaction, and after 10 min of reaction corresponding to *ca.* 34% yield using the [Pd]/SBA-15 catalyst (or alternatively, 20 min of reaction, *ca.* 22% yield for the $[Pd(NH_3)_4]^{2+}$/NaY), the reaction mixture was filtered through a celite pad to afford a clear filtrate. The clear filtrate was then treated as the

Table 2. Recycling studies of the heterogeneous palladium catalysts for the one-pot synthesis of 2-phenylindoles (Scheme 1).

Run	Conversion [%][a]	
	$[Pd(NH_3)_4]$/NaY	[Pd]/SBA-15
1	100	100
2	87	93
3	72	87
4	20	68
5	<5	48
6	Not evaluated	24

Reaction conditions: 5 mmol 2-iodoaniline, 7 mmol phenylacetylene, 8 mmol Et_3N, 1 mol % [Pd] catalyst, 10 mL DMF/H_2O (4:1), 80 °C, 6 h.

[a] Conversions based on unreacted aryl halide. The selectivity of the reaction is > 95%, i.e., in the error range of the analytical method.

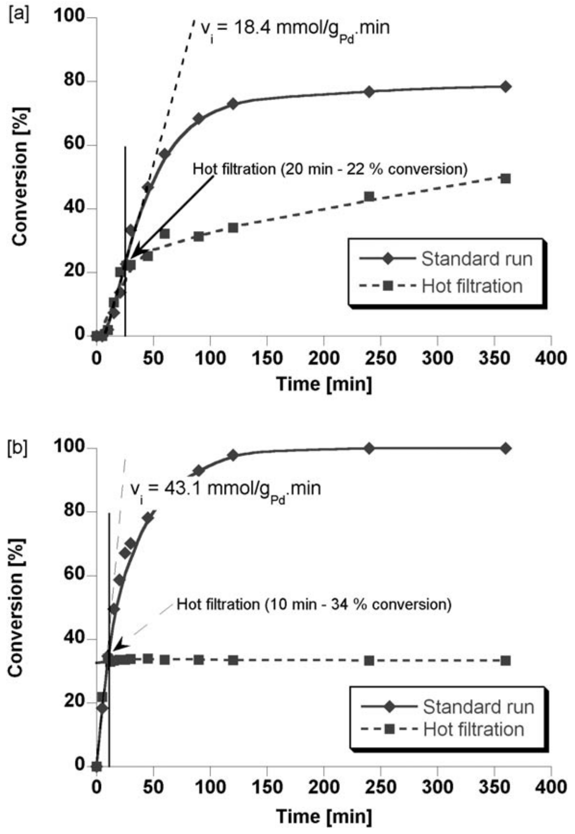


Figure 2. Leaching of active Pd species in solution: [**a**] using $[Pd(NH_3)_4]$/NaY and [**b**] using [Pd]/SBA-15 catalyst. *Reaction conditions:* 5 mmol 2-iodoaniline, 7 mmol phenylacetylene, 8 mmol Et_3N, 1 mol % [Pd] catalyst, 10 mL DMF/H_2O (4:1), 80 °C.

usual catalytic test, and its composition was followed by GC and compared to that of a standard catalytic run.

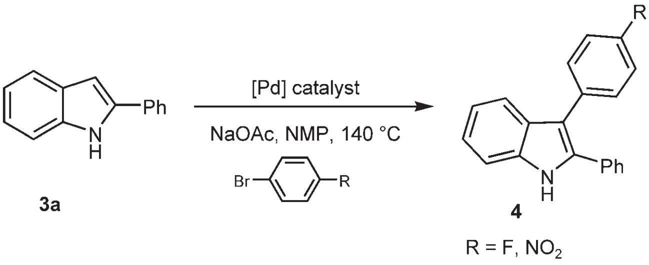
Figure 2 shows clearly that the catalytic activity observed using the $[Pd(NH_3)_4]^{2+}$/NaY catalyst is mainly due to dissolved active Pd species since the conversion of the 2-iodoaniline after the hot filtration increased from 22% to 50%. However, one should note that the overall activity observed for the clear filtrate is not as high as that observed in the presence of the heterogeneous catalyst that can be seen as a "continuous" source of active Pd species. This result contrasts with that obtained from AAS analyses of the clear supernatant solutions while evaluating the recycling, attesting clearly that dissolution-redeposition equilibrium occurs during such coupling reactions, as has often been suggested in the literature. This equilibrium is therefore clearly dependent on the reaction temperature, and strongly displaced towards the redeposition at low (ambient) temperatures.

On the contrary, the results obtained using the [Pd]/SBA-15 catalyst clearly showed that no leaching of active Pd species in the bulk solution occurred indicating that the activity observed for that mesoporous based catalyst is really due to the heterogeneous catalyst.

AAS analyses of the clear filtrates obtained by hot filtration are in good agreement with these results: a Pd content of 1150 ppm was determined for the catalytically active filtrate recovered from the $[Pd(NH_3)_4]^{2+}$/NaY-catalysed reaction which can be compared to that of <0.5 ppm for the filtrate recovered from the [Pd]/SBA-15-catalysed reaction (which was shown to be inactive).

Extended Applications

Having demonstrated the potential of the heterogeneous $[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15 catalysts for the synthesis of 2-functionalised indoles **3**, we were interested in examining the possibility of arylating 2-substituted indoles at the 3-position of the ring (Scheme 2, Table 3). Initially, we chose to study the arylation of 2-phenylindole under standard cross-coupling conditions (5 mmol 2-phenylindole, 7 mmol aryl halide, 7 mmol NaOAc, 1 mol % [Pd], 10 mL NMP, 140 °C).



Scheme 2. Cross-coupling arylation at the 3-position of the 2-phenylindole.

As reported in Table 3, the arylation of 2-phenylindole (**3a**) catalysed by the homogeneous $Pd(OAc)_2$, while being possible, is a very slow reaction requiring up to 12 days for the half conversion of the 2-phenylindole into the expected arylated compound **4**, independently of the aryl halide used. However, this reaction was limited to the use of highly reactive electron-deficient aryl bromides that are reputed to give high reaction rates in related Heck coupling reactions. Surprisingly, the homogeneous palladacyle gave almost no conversion (only 3% after 6 days for the reaction with 4-bromofluorobenzene) which was attributed to steric hindrance in the coordination sphere of the palladium(II) transition state. Interestingly, the use of the heterogeneous [Pd]/SBA-15 catalyst did not significantly decrease the reaction rate, which remains in an acceptable range. On the other hand, the $[Pd(NH_3)_4]^{2+}$/NaY catalyst gave only low conversions, probably due to diffusion limitations or to the formation of less active palladium agglomerates into the bulk solution (leaching).

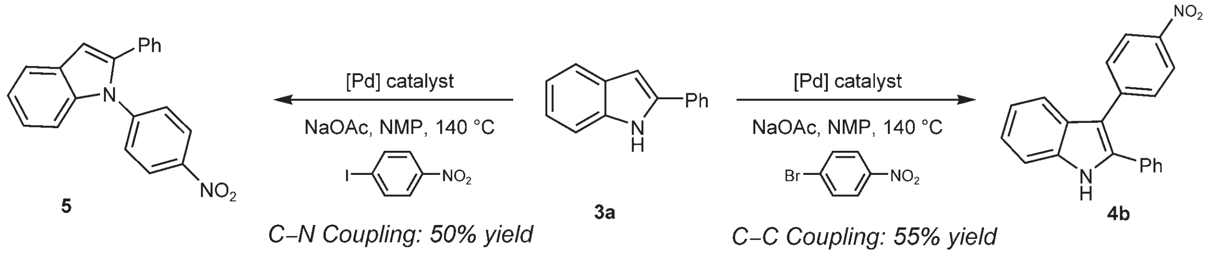
Table 3. Palladium-catalysed, one-pot synthesis of 2,3-functionalised indoles (Scheme 2).

Product	R	Catalyst	Time [days]	Conversion [%][a]	GC Yield [%][a]
4a	F	$Pd(OAc)_2$	12	50	48 (40)
		Palladacycle[b]	*6*	*3*	–
		$[Pd(NH_3)_4]/NaY$	12	8	7
		[Pd]/SBA-15	12	38	35
4b	NO_2	$Pd(OAc)_2$	12	55	55 (39)
		$[Pd(NH_3)_4]/NaY$	12	7	7
		[Pd]/SBA-15	12	41	36

Reaction conditions: 2 mmol indole, 2.2 mmol aryl halide, 2.2 mmol NaOAc, 1 mol % [Pd] catalyst, 8 mL NMP, 140 °C.

[a] Conversions based on unreacted aryl halide and yields were determined by GC with an internal standard (diethylene glycol di-*n*-butyl ether) ($\Delta_{rel} = \pm 5\%$). Values in parentheses correspond to isolated product yields.

[b] Given the very low activity of this catalyst, it was not further evaluated for this reaction.



Scheme 3. Dual reactivity in the 2-phenylindole: C–C *versus* C–N coupling reactions.

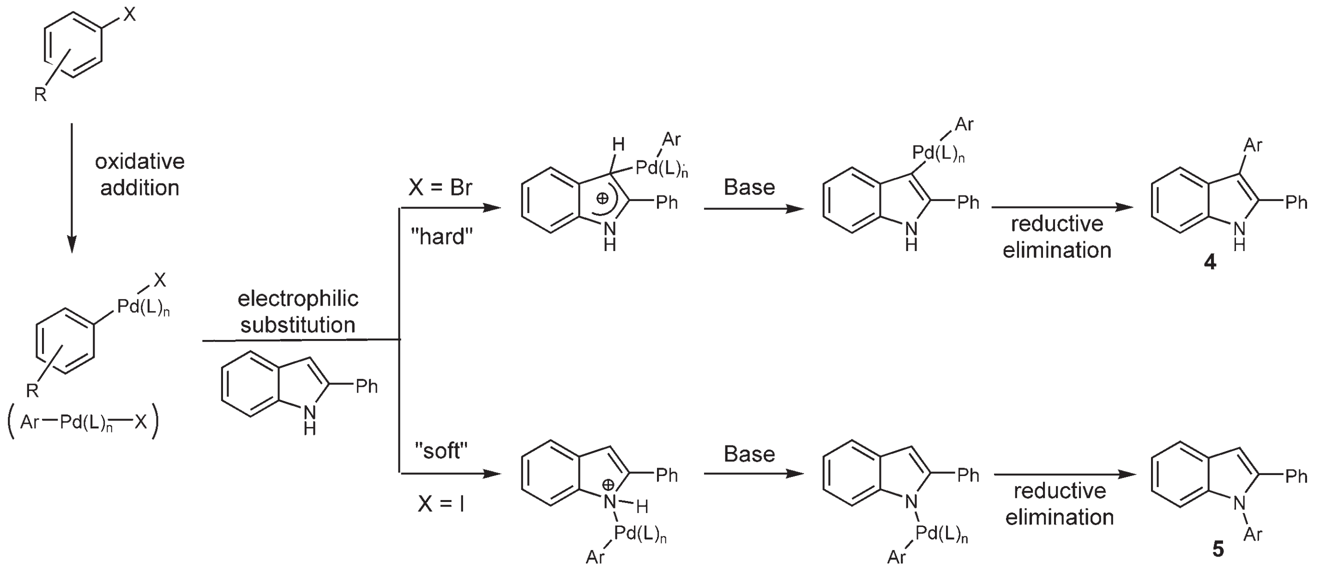
The reactivity of the aryl halides in the Heck reaction being well established to follow the order I > Br, we decided to use the more reactive 4-iodonitrobenzene. Unexpectedly, using the iodo derivative, we did not observe the C–C coupling reaction as with the 4-bromonitrobenzene or the 4-bromofluorobenzene to give **4a**, **b**, but rather a clean C–N coupling reaction between the 2-phenylindole (**3a**) and the aryl iodide to give the compound **5** (Scheme 3).

Similar arylation reactions of indole derivatives catalysed by homogeneous palladium complexes were recently reported by Sames et al.[45–48] Under their reaction conditions [$Pd(OAc)_2$, PPh_3, MgO, PhI, polar solvent, 125–150 °C, 24 h], exclusively C2-arylation of NH-"free" indoles was observed. The authors explained this selectivity by the *in situ* formation of an indole-magnesium salt (*N*-MgX) which acts as a protecting group of the nitrogen site. In some cases, C3-arylation was also shown depending on the magnesium source and the solvent.

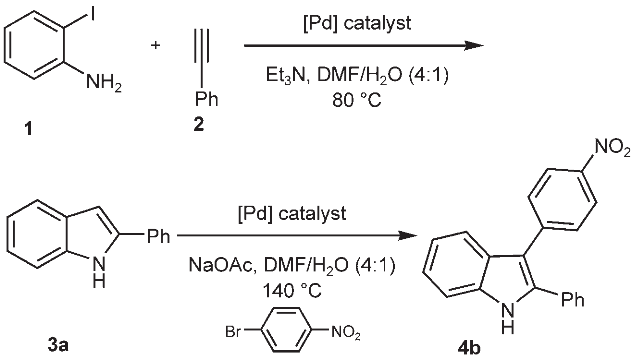
In our case (Pd catalyst, NaOAc, ArX, polar solvent, 140 °C), since the C2-position is already blocked by a phenyl substituent, two sites of arylation could be considered: the C3-postion of the azole ring (C–C coupling) and the N1-position (C–N coupling)[49] since no N-protecting group (i.e., alkyl susbtituent...) or agent (i.e., magnesium source...) is used leaving this site accessible to the arylation reaction.

The best explanation to account for the observed selectivity between aryl iodide and aryl bromide compounds in the arylation of the 2-phenylindole is to consider the electrophilic substitution mechanism previously reported by Gevorgyan et al.[50] and Sames et al.[48] for heteroaromatic compounds (Scheme 4). The first step involves an oxidative addition between palladium(0) species and the aryl halide which leads to an aryl-palladium(II) intermediate. Depending on the nature of the halide, the palladium centre could be seen as a "hard" (case of the bromide) or a "soft" (case of the iodide) electrophile. In the former the electrophilic substitution of the bromide would involve the olefinic position leading to arylation at the C3-position whereas in the case of the iodide the electrophilic substitution would imply the nitrogen atom giving rise to arylation at the N1-position. The last steps involve a deprotonation and a reductive elimination of palladium(0) species.

Given these encouraging results, we undertook the evaluation of a one-pot synthesis of the 2,3-functionalised indole, **4**, from 2-iodoaniline based on these heterogeneous catalysts (Scheme 4). The first reaction involves the condensation with phenylacetylene, which was fully achieved after 24 h using 5 mol % [Pd]/SBA-15 catalyst under the previously defined reaction conditions. The second step was then initiated without any separation of the intermediates, that is by the addition into the reaction mixture of the corresponding amounts of 4-bromofluorobenzene and sodium acetate. The result was disappointing as only 8% conversion of the intermediate 2-phenylindole (**3a**) was achieved within 8 days to give the expected compound **4b**, after which no



Scheme 4. Proposed pathways to account the selectivity observed in the Pd-catalysed arylation of 2-phenylindole by aryl bromides or iodides.



Scheme 5. Direct one-pot synthesis of 2,3-substituted indoles.

evolution was observed. However, we should mention that the reaction used here, and particularly the solvent used (DMF/H_2O, 4:1), did not correspond to optimised cross-coupling conditions.

Conclusions

In summary, we have demonstrated the efficiency of heterogeneous palladium catalysts ($[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15) for the synthesis of 2-functionalised indoles, **3**. Generally high conversions and selectivities are observed, leading to moderate to high isolated yields using 1 mol % [Pd] catalyst. Standard reaction conditions were defined in order to be independent of the substrate; however, some of these reactions were found to be quite slow (up to 2 days) and require further optimisation. We also demonstrated that the arylation of 2-phenylindole under classical cross-coupling reaction conditions was possible, but these reactions were, predictably, very slow. While trying to improve this step by using a more reactive aryl iodide, we discovered a duality of reactivity in the indole nucleus: using aryl bromides a clean C–C coupling reaction was observed while using the corresponding aryl iodide led to a clean C–N coupling reaction.

Further studies are concentrating on the optimisation all reaction steps (reaction conditions, catalysts...) and to develop a direct one-pot synthesis of 2,3-funtionalised indoles starting from simple 2-iodoaniline, alkynes and aryl halides.

Experimental Section

General Remarks

All manipulations were conducted under a strict inert atmosphere or vacuum conditions using Schlenk techniques including the transfer of the catalysts to the reaction vessel. All glassware was base- and acid-washed and oven-dried.

The solvents used for the synthesis of the molecular palladium precursors and catalysts were dried using standard methods and stored over activated 4 Å molecular sieves. All other chemicals (organic reagents and solvents) were deaerated by an argon flow before they were used.

Tetraethoxysilane (TEOS), poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymer (Pluronic 123, Mw: 5000) and diethoxymethylvinylsilane were purchased from Aldrich Chemical and used without further purification. $PdCl_2$ and $PdCl_2(PPh_3)_2$ were obtained, respectively, from Alfa and Strem Chemicals. Diphenylphosphine was supplied by Fluka. 2-(Diphenylphosphino)ethyldiethoxymethylsilane, PPh_2-$(CH_2)_2$-$SiCH_3(OCH_2CH_3)_2$, was synthesised by adapting the procedure reported by Schmid et al.[51] Equimolar quantities of $HPPh_2$ and diethoxymethylvinylsilane were irradiated for 4 days using a UV light (high pressure Hg lamp) and a water-cooled quartz reactor; the product was purified by distillation under vacuum (bp 170–180 °C/0.1 Torr, 85% yield). The NaY zeolite (LZ-Z-52) was purchased from Sigma-Aldrich Chemicals. The *N*-tosyl-2-idodoaniline was prepared according a procedure reported in the literature.[30]

Characterisation

All solid-state NMR spectra were recorded on a Bruker DSX-300 or Avance-500 spectrometer equipped with a standard 4 mm probehead. The spinning rate was typically 10 kHz. ^{13}C, ^{29}Si and ^{31}P NMR spectra were obtained by use of cross-polarisation (contact time 5 ms). To achieve a good polarisation transfer, a ramp was used on the X channel. Recycle delays were typically 1 s (a study on the ^{1}H nucleus showed that it was sufficient to allow all protons to fully relax). ^{1}H, ^{13}C and ^{29}Si MAS spectra were referenced to tetramethylsilane. ^{31}P MAS spectra were referenced to 85% H_3PO_4.

X-ray powder diffraction (XRD) data were acquired on a Bruker D5005 diffractometer using Cu K_α radiation (λ = 1.54184 E). A TA Instruments thermoanalyser 2950 HR V5.3. was used for simultaneous thermal analysis combining thermogravimetric (TGA) and differential thermoanalysis (DTA) at a heating rate of 5 °C/min in air. Nitrogen adsorption and desorption isotherms were measured at 77 K. The organometallic-inorganic hybrids were evacuated at 160 °C for 24 hours before the measurements. Specific surface areas were calculated following the BET procedure. Pore size distribution was obtained by using the BJH pore analysis applied to the desorption branch of the nitrogen adsorption/desorption isotherm.

The palladium content determinations of the heterogeneous catalysts {$[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15} were performed by ICP-AES from a solution obtained by treatment of the catalysts with a mixture of HBF_4, HNO_3 and HCl in a Teflon reactor at 180 °C.

Liquid NMR spectra were recorded on a Bruker AC-250 spectrometer. All chemical shifts were measured relative to residual ^{1}H or ^{13}C NMR resonances in the deuterated solvents: $CDCl_3$, $\delta = 7.25$ ppm for ^{1}H, 77 ppm for ^{13}C. Flash chromatography was performed at a pressure slightly greater than atmospheric pressure using silica (Merck Silica Gel 60, 230–400 mesh). Thin layer chromatography was performed on Fluka Silica Gel 60 F_{254}.

High resolution mass spectra (HR-MS) were recorded on a Thermo Finnigan MAT 95 XL spectrometer, with isobutane as reactant gas for CI.

GC analyses were performed on an HP 4890 chromatograph equipped with an FID detector, an HP 6890 autosampler and an HP-5 column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness). Nitrogen was used as carrier gas. The mass spectra were obtained on an HP 6890 gas chromatograph equipped with an HP 5973 mass detector and an HP-5 MS column (cross-linked 5% phenyl-methylsiloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness). Helium was used as carrier gas. The experimental error was estimated to be $\Delta_{rel} = \pm 5\%$.

Catalyst Preparation

The homogeneous "palladacycle" $\{Pd[P(o\text{-}C_6H_4CH_3)_2\text{-}(C_6H_4CH_2)][OCOCH_3]\}_2$ catalyst was prepared from $Pd(OAc)_2$ and tri(*o*-tolyl)phosphine following the procedure reported by W. A. Herrmann et al.[52] The $PdCl_2(PhCN)_2$ used as palladium precursor for the preparation of the [Pd]/SBA-15 catalyst was prepared according to procedures previously described in the literature.[53] The $PdCl_2\{PPh_2\text{-}(CH_2)_2\text{-}SiCH_3(OCH_2CH_3)_2\}_2$ was synthesized by reacting 2 equivalents of $PPh_2\text{-}(CH_2)_2\text{-}SiCH_3(OCH_2CH_3)_2$ with bis(benzonitrile)palladium dichloride at room temperature in dichloromethane by adapting a procedure reported elsewhere.[54]

Preparation of $[Pd(NH_3)_4]^{2+}$/NaY[41]

A 0.1 M ammonia solution of $[Pd(NH_3)_4]Cl_2$ – prepared from $PdCl_2$ and a commercial ammonia solution – was added dropwise (4 mL/g zeolite, corresponding to *ca.* 5% wt Pd in the final catalyst) to a suspension of the zeolite NaY in bidistilled water (100 mL/g zeolite). The mixture was stirred for 24 h at room temperature and the exchanged zeolite was filtered off and washed until no trace of chloride was detected in the filtrate ($AgNO_3$ test). Then the zeolite was allowed to dry at room temperature to give the entrapped $[Pd(NH_3)_4]^{2+}$/NaY catalyst as slightly yellow material. ICP-AES analysis: 4.8% wt Pd.

Preparation of [Pd]/SBA-15[42]

Mesoporous SBA-15 type silica was used as support and was prepared by the acid-catalysed, non-ionic assembly pathway described by Margolese et al.[55] The structure directing agent (Pluronic 123) was removed by calcination under air at 500 °C and the surfactant-free mesoporous silica was rigorously dried under a flow of nitrogen at 200 °C prior to the grafting reaction. Typically, $PdCl_2\{PPh_2\text{-}(CH_2)_2\text{-}SiCH_3(OCH_2CH_3)_2\}_2$ (~500 mg) dissolved in dry toluene was added dropwise to a suspension of calcined SBA-15 (1 g) in toluene and stirred at 25 °C for two hours to allow the diffusion of the molecular precursor into the channels of the pores. The reaction mixture was then heated at 85 °C overnight. After filtration of the solid, the unreacted palladium precursor was removed by a Soxhlet extraction with CH_2Cl_2 during 10 hours. Finally, the resulting solid was dried in vacuum at 25 °C. The organometallic-inorganic hybrid material, denoted [Pd]/SBA-15, has been characterised by several analytical, physical and spectroscopic techniques including small-angle X-ray powder diffraction, nitrogen sorption isotherms, solid-state ^{1}H, ^{13}C, ^{31}P and ^{29}Si NMR spectroscopy and TG-analyses (see Supporting Information). ICP-AES analysis: 2.1% wt Pd and 1.3% wt P; MAS ^{1}H NMR: $\delta = 0.6$ ($-SiCH_3$, $-SiCH_2CH_2P$, $-OCH_2CH_3$), 3.3 ($-SiCH_2CH_2P$, $-OCH_2CH_3$), 6.7 (phenyl ring); CP-MAS ^{13}C NMR: $\delta = -4.6$ ($-SiCH_3$), 10.5 ($-SiCH_2CH_2P$), 18.7 and 20.1 ($-OCH_2CH_3$ and $-SiCH_2CH_2P$, respectively), 58.2 ($-OCH_2CH_3$), 129.7–137.8 (phenyl ring); CP-MAS ^{29}Si NMR: $\delta = -12.6$ (D^1 and D^2 sites), -91.6 (Q^2 sites), -101.4 (Q^3 sites), -108.2 ppm (Q^4 sites); CP-MAS ^{31}P NMR: $\delta = 20.7$ (*trans* isomer), 30.9 (*cis* isomer).

Catalytic Tests

The catalytic reactions were carried out in a three-necked flask, or alternatively in pressure-sealed tubes, under argon. The qualitative and quantitative analysis of the reactants and the products was made by gas chromatography. Conversion and yields were determined by GC based on the relative area of GC signals referred to an internal standard (diethylene glycol di-*n*-butyl ether) calibrated to the corresponding pure compound. All catalysts were handled and transferred under argon.

General Procedure for the Synthesis of 2-Functionalised Indoles 3

A total of 5 mmol of 2-iodoaniline (1.09 g) or *N*-tosyl-2-iodoaniline (1.96 g), 7 mmol of alkyne, 8 mmol of Et_3N (809 mg, 1.03 mL) and 1 mol % [Pd] catalyst was introduced in a three-necked flask (or in a pressure-sealed tube) under argon. Then 10 mL of DMF/H_2O (4:1) (previously deaerated) was added and the mixture was further deaerated by an argon flow for 5 min. The reactor was placed in a preheated oil bath at 80 °C. The reaction was conducted under vigorous stirring and then the reaction mixture was cooled to room temperature.

The reaction mixture was then diluted with 250 mL of water and the resulting mixture was extracted with 4 × 20 mL CH_2Cl_2 or ethyl acetate. The combined organic layers were washed three times with 15 mL H_2O, once with 15 mL brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel. The isolated compound **3a**, **3b**, **3c**, **3e** and **3g** gave NMR and mass spectroscopic data in accordance with the literature.[56–61] All other 2-functional indoles **3** were fully characterised through ^{1}H and ^{13}C NMR, elemental analysis, GC-MS and HR-MS (data are available in the Supporting Information).

General Procedure for the Synthesis of 2,3-Functionalised Indoles by Cross-Coupling Reaction

A total of 2 mmol of 2-phenylindole (384 mg), 2.2 mmol of aryl halide, 2.2 mmol of NaOAc (180 mg) and 1 mol % [Pd] catalyst was introduced in a pressure-sealed tube under argon. Then 8 mL of NMP (previously deaerated) was added and the mixture was further deaerated by an argon flow for 5 min. The reactor was placed in a preheated oil bath at 140 °C. The reaction was conducted under vigorous stirring and then the reaction mixture was cooled to room temperature.

The reaction mixture was then diluted with 150 mL of water and the resulting mixture was extracted with 3 × 20 mL of ethyl acetate. The combined organic layers were washed three times with 15 mL H_2O, once with 15 mL brine, dried over $MgSO_4$ and evaporated. The residue was then purified by flash chromatography on silica gel. Indoles **4** and **5** were fully characterised through ^{1}H and ^{13}C NMR, elemental analysis, GC-MS and HR-MS (data are available in the Supporting Information).

Acknowledgements

Financial support provided by the Région Rhône-Alpes, France (Contract "NAHMOVCA" Number 301439201/E038131747/ENS006) is gratefully acknowledged.

References

[1] R. J. Sundberg, *Indoles*, Academic Press, London, **1996**.
[2] J. A. Joule, in: *Science of Synthesis, Vol. 10*, (Ed.: E. J. Thomas), Thieme, Stuttgart, **2001**, p. 361.
[3] R. J. Sundberg, in: *Comprehensive Heterocyclic Chemistry, Vol. 4*, (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, p. 313.
[4] J. Tois, R. Franzén, A. Koskinen, *Tetrahedron* **2003**, *59*, 5395.
[5] D. Hughes, *Org. Prep. Proceed. Int.* **1993**, *25*, 607.
[6] B. Robinson, *The Fischer Indole Synthesis*, John Wiley & Sons, Chichester, **1982**.
[7] R. D. Clark, D. B. Repke, *Heterocycles* **1984**, *22*, 195.
[8] P. D. Johnson, P. A. Aristoff, *J. Org. Chem.* **1990**, *55*, 1374.
[9] S. W. Wright, L. D. McClure, D. L. Hageman, *Tetrahedron Lett.* **1996**, *37*, 4631.
[10] F. Piozzi, M. R. Langella, *Gazz. Chim. Ital.* **1963**, *93*, 1382.
[11] W. J. Houlihan, Y. Uike, V. A. Parrino, *J. Org. Chem.* **1981**, *46*, 4515.
[12] D. A. Wacker, P. Kasireddy, *Tetrahedron Lett.* **2002**, *43*, 5189.
[13] G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* **2002**, 2671.
[14] S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873.
[15] R. C. Larock, S. Babu, *Tetrahedron Lett.* **1987**, *28*, 5291.
[16] R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689.
[17] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652.
[18] G. Huang, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 7342.
[19] K. Iritani, S. Matsubara, K. Uchimoto, *Tetrahedron Lett.* **1988**, *29*, 1799.
[20] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1992**, *33*, 3915.
[21] S. Cacchi, G. Fabrizi, L. M. Parisi, *Heterocycles* **2002**, *58*, 667.
[22] S. Cacchi, G. Fabrizi, D. Lamba, F. Marinelli, L. M. Parisi, *Synthesis* **2003**, 728.
[23] S. L. Hegedus, G. F. Allen, J. J. Bozell, E. L. Waterman, *J. Am. Chem. Soc.* **1978**, *100*, 5800.
[24] R. C. Larock, S. Babu, *Tetrahedron Lett.* **1987**, *28*, 1037.
[25] A. Takeda, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 5662.
[26] A. J. Peat, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 1028.
[27] S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 10251.

[28] M. Watanabe, T. Yamamoto, M. Nishiyama, *Angew. Chem. Int. Ed.* **2000**, *39*, 2501; *Angew. Chem.* **2000**, *112*, 2620.

[29] L. Ackermann, *Org. Lett.* **2005**, *7*, 439.

[30] B. Witulski, C. Alayrac, L. Tevzadze-Saeftel, *Angew. Chem. Int. Ed.* **2003**, *42*, 4257; *Angew. Chem.* **2003**, *115*, 4392.

[31] N. Suzuki, S. Yasaki, A. Yasuhara, T. Sakamoto, *Chem. Pharm. Bull* **2003**, *51*, 1170.

[32] S. Cacchi, G. Fabrizi, L. M. Parisi, *Org. Lett.* **2003**, *5*, 3843.

[33] N. Sakai, K. Annaka, T. Konakahara, *Org. Lett.* **2004**, *6*, 1527.

[34] M. C. Fagnola, I. Candiani, G. Visentin, W. Cabri, F. Zarini, N. Mongelli, A. Bedeschi, *Tetrahedron Lett.* **1997**, *38*, 2307.

[35] H.-C. Zhang, K. K. Brumfield, B. E. Maryanoff, *Tetrahedron Lett.* **1997**, *38*, 2439.

[36] H.-C. Zhang, H. Ye, A. F. Moretto, K. K. Brumfield, B. E. Maryanoff, *Org. Lett.* **2000**, *2*, 89.

[37] S. Chouzier, M. Gruber, L. Djakovitch, *J. Mol. Catal. A: Chem.* **2004**, *212*, 43.

[38] M. Gruber, S. Chouzier, K. Koehler, L. Djakovitch, *Appl. Catal. A: Gen.* **2004**, *265*, 161.

[39] M. Pal, V. Subramanian, V. R. Batchu, I. Dager, *Synlett* **2004**, 1965.

[40] K. B. Hong, C. W. Lee, E. K. Yum, *Tetrahedron Lett.* **2004**, *45*, 693.

[41] L. Djakovitch, K. Koehler, *J. Am. Chem. Soc.* **2001**, *123*, 5990.

[42] P. Rollet, W. Kleist, V. Dufaud, L. Djakovitch, *J. Mol. Catal. A: Chem.* **2005**, *241*, 39.

[43] L. Djakovitch, P. Rollet, *Adv. Synth. Catal.* **2004**, *346*, 1782.

[44] W. Wang, T. Ikemoto, *Tetrahedron Lett.* **2005**, *46*, 3875.

[45] B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2003**, *125*, 5274.

[46] B. S. Lane, D. Sames, *Org. Lett.* **2004**, *6*, 2897.

[47] X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996.

[48] B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050.

[49] B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599.

[50] J. T. Kim, J. Butt, V. Gevorgyan, *J. Org. Chem.* **2004**, *69*, 5638.

[51] L. Schmid, O. Kröcher, R. A. Köppel, A. Baiker, *Microporous and Mesoporous Mater.* **2000**, *35–36*, 181.

[52] M. Beller, H. Fischer, W. A. Herrmann, K. Öfele, C. Broßmer, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1848. *Angew. Chem.* **1995**, *107*, 1992.

[53] M. R. Karasch, R. C. Seyler, F. R. Mayo, *J. Am. Chem. Soc.* **1938**, *60*, 882.

[54] R. A. Komoroski, A. J. Magistro, P. P. Nicholas, *Inorg. Chem.* **1986**, *25*, 3917.

[55] D. Margolese, J. A. Melero, S. C. Christiansen, B. F. Chmelka, G. D. Stucky, *Chem. Mater.* **2000**, *12*, 2448.

[56] C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron* **2003**, *59*, 1571.

[57] C. Amatore, E. Blart, J. P. Genet, A. Jutand, S. Lemaire-Audoire, M. Savignac, *J. Org. Chem.* **1995**, *60*, 6829.

[58] K. Hiroya, S. Itoh, T. Sakamoto, *J. Org. Chem.* **2004**, *69*, 1126.

[59] J. Bergman, P. O. Norrby, U. Tilstam, L. Venemalm, *Tetrahedron* **1989**, *45*, 5549.

[60] K. Mohri, Y. Oikawa, K. Hirao, O. Yonemitsu, *Heterocycles* **1982**, *30*, 3097.

[61] K. Mohri, Y. Oikawa, K. Hirao, O. Yonemitsu, *Heterocycles* **1982**, *19*, 515.