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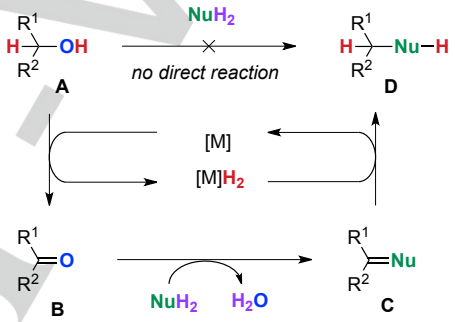
# Catalytic *C*-Alkylation of Pyrroles with Primary Alcohols: Hans Fischer's Alkali, and a New Spin with Iridium *P,N,P*-Pincer Complexes

Sebastian Koller,[a] Max Blazejak,[a] and Lukas Hintermann*[a]

**Abstract:** Hydrogen autotransfer alkylation (HAT or "borrowing hydrogen" alkylation) of heteroaromatic compounds has been studied with a range of substrates recently, but pyrroles have been largely absent from such studies. The conditions for HAT-alkylations of pyrroles were investigated under a variety of conditions and found to take place a) under basic alcoholic conditions (*Hans-Fischer-alkylation*) in the absence of transition metal catalysts; b) by means of a heterogeneous Pd/C catalyst in the presence of base; c) and finally by means of homogeneous transition metal catalysis combining base and *in situ* generated iridium pincer complexes introduced by Kempe and not previously used in HAT-alkylations of heterocycles.

## Introduction

Catalytic reactions involving hydrogen autotransfer (HAT) from starting materials to products (i.e., following the *"borrowing hydrogen principle"*) have recently become a useful tool for C–C and C–N bond formation in organic chemistry.[1,2] Such transformations generate water as sole stoichiometric byproduct and, by virtue of their high atom-economy, can be important contributors to green chemistry. The principle of HAT-alkylation of a nucleophile ($H_2Nu$; both hydrogens need not be attached at the same nucleophilic center, since one may be in a tautomeric position) with alcohol **A** is illustrated in Scheme 1: Catalyst-mediated dehydrogenation of **A** gives carbonyl compound **B** and reduced catalyst $[M]H_2$; this is followed by spontaneous or bas-catalyzed condensation of **B** with the nucleophile to give unsaturated intermediate **C**; the latter is subsequently hydrogenated by $MH_2$ to give product **D**, thereby regenerating catalyst [M] in the process. These reactions are typically conducted with a transition-metal catalyst (*viz.* Ir, Ru) capable of hydrogen-transfers, and a base co-catalyst for the condensation step. Such methodology has been applied to *C*-alkylation via activation of the acidified $\alpha$-C($sp^3$)-H-bonds of carbonyl compounds (ketones, esters, amides), nitriles or other substrates.[2] However, *C*-alkylation with alcohols is also possible at C($sp^2$)-centers of electron-rich (hetero)aromatic cores: with indoles, regioselective C-3-alkylation has been realized using base and the catalysts $[Cp^*IrCl_2]_2$,[3a,b,c] $RuCl_2(PPh_3)_2$/DPE-Phos,[3d] Pd/C,[3d] Pt nanoclusters;[4] for the related case of indole HAT-alkylation with amines as alkylating agents, the use of Shvo's catalyst[5a] or of a redox-active anthraquinone/amine organocatalyst has been described.[5b,6]




**Scheme 1.** General mechanistic sequence for a HAT-alkylation.

Recently, HAT-*C*-alkylations have also been realized with phenols as examples of non-heterocyclic arenes.[7] Notwithstanding the success of such protocols, remarkably, HAT-alkylation with alcohols and alkali base as *sole* catalyst have been described, where hydride-transfers appear to proceed *via* Cannizarro-type mechanisms.[8] Such transition-metal free HAT-alkylations were described for ketones[9] and electron-rich *N*-heterocycles including indoles.[10,11]

In contrast to numerous studies on indoles, HAT-alkylation of pyrroles has been nearly absent; while our work was in progress, an example of methylation of pyrroles by methanol (140 °C, pressure tube) using $[Cp^*IrCl_2]_2$ as catalyst was reported.[12] However, we have become aware of work performed by Hans Fischer and coworkers in 1912, describing remarkable alkylations of simple pyrroles in alcoholic sodium alkoxide at elevated temperature in sealed tubes (Scheme 2, a).[13] A table with reaction examples reported by Fischer has been compiled in the supporting information (Table S-1).

Hans Fischer's lifework on the structure elucidation and synthesis of pyrrole pigments was highlighted by the award of the 1930 Nobel Prize of chemistry *"for his researches into the constitution of haemin and chlorophyll and especially for his synthesis of haemin"*.[14] He was a leading authority on the chemistry of pyrroles, and a monograph, written with H. Orth and A. Stern,[15] remained a key reference for many years, and continues to be referenced in contemporary work.[16,17] The alkoxide-mediated alkylation of pyrroles was among Fischer's

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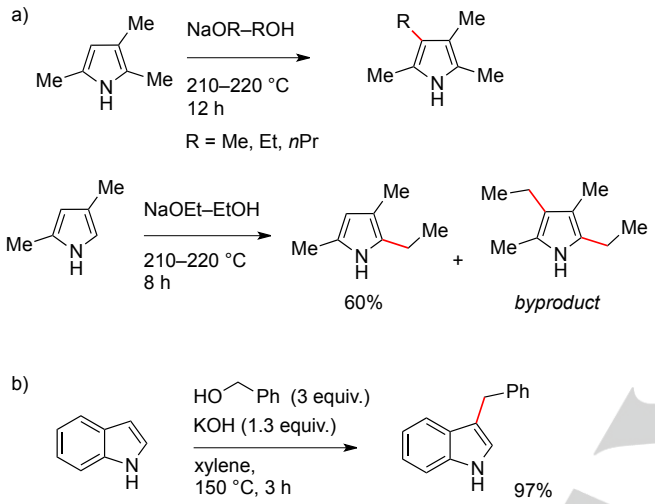
earliest contributions to pyrrole chemistry and was immediately applied for structural proof (through synthesis) of a series of alkylated pyrroles, which had been obtained by degradation from blood pigment.[18] The mechanism of this reaction was unknown at the time of discovery[13a] and was still considered an unsolved riddle 60 years later.[19,20] In view of recent developments in HAT-alkylation chemistry with alkali bases, particularly the related alkylation of indoles (Scheme 2, b)[10,11] or the base-mediated alkylation of ketones,[9] a new interpretation of the Hans-Fischer-alkylation as hydrogen autotransfer (HAT) reaction recommended itself.



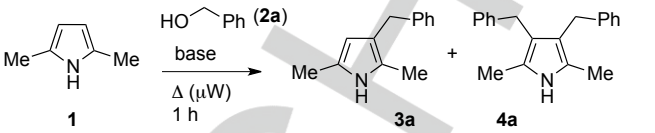

**Scheme 2.** a) Pyrrole alkylations mediated by alcoholic alkoxide as performed by Hans Fischer.[13] b) Base-induced HAT-alkylation of indole.[10]

Our study aimed at addressing two key questions: first, to collect evidence for the HAT-nature of the Hans-Fischer-alkylation, and second, to take advantage of more recent knowledge of transition metal-catalyzed HAT-alkylations to establish catalytic HAT-*C*-alkylation protocols for pyrroles that will possibly proceed under milder reaction conditions. In view of the importance of pyrroles as structural motifs in pharmacologically active compounds, an extension of the synthetic repertoire for pyrrole alkylation by simple and atom-economic methods is highly desirable.

## Results and Discussion

Pyrrole alkylations according to Hans Fischer were performed in sealed tubes (*"Carius bomb tubes"*) and had a high incidence of explosive bursts.[21] To simulate the original reaction conditions in a reliable way we used microwave irradiation under adiabatic conditions, and with high-boiling alcohols to limit pressure buildup. Heating of 2,5-dimethylpyrrole (**1**) with benzyl alcohol (**2a**) and base to 250 °C produced mono- (**3a**) as well as dibenzylated (**4a**) product under a variety of conditions (Table 1).

**Table 1.** Base-mediated pyrrole alkylation under microwave conditions.[a]

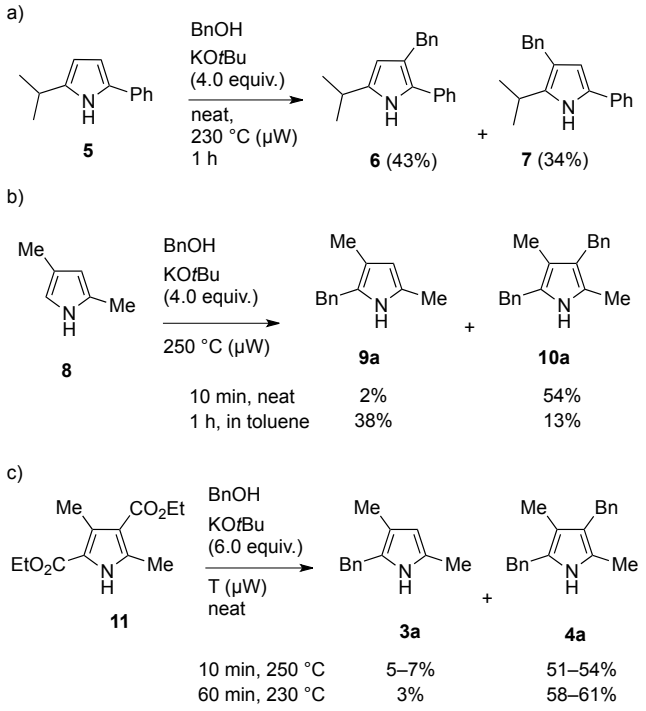



| Entry | Base (equiv.) | BnOH (equiv.) | Solvent | T [°C] | **3a**[b] [mol%] | **4a**[b] [mol%] |
|---|---|---|---|---|---|---|
| 1 | NaH (2) | 19 | neat | 250 | 51 | 19 |
| 2 | KOH (2) | 19 | neat | 250 | 36 | 18 |
| 3 | NaOH (2) | 19 | neat | 250 | 52 | 10 |
| 4 | LiOBn[c] (2) | 19 | neat | 250 | 27 | 0 |
| 5 | KO*t*Bu (2) | 19 | neat | 250 | 31 | 54 |
| 6 | KO*t*Bu (4) | 19 | neat | 250[d] | 8 | 60 |
| 7 | KO*t*Bu (4) | 6 | toluene | 250[d] | 61 | 19 |
| 8 | KO*t*Bu (4) | 6 | toluene | 240 | 48 | 21 |

[a] Reaction scale: 1.0 mmol. [b] Analytical yield determined by qNMR against internal standard. [c] Base was prepared in situ by dissolving Li metal in BnOH at 70 °C. [d] Temperature was automatically reduced over reaction time to prevent exceeding the reactor pressure limit (30 bar).

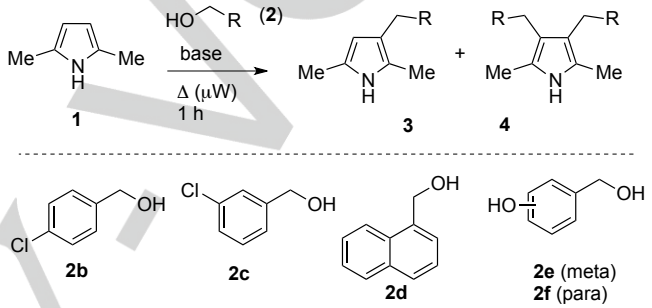
KO*t*Bu was in general superior (Table 1, entries 5–8) over sodium (entries 1, 3) or lithium (entry 4) bases. A large excess of benzyl alcohol (**2a**) – which also serves as the solvent – in combination with KO*t*Bu favors dialkylation (entries 5, 6), but a sixfold excess of alcohol in toluene favors monobenzylated product **3a** (entries 7, 8). More polar solvents (dioxane, diglyme) gave inferior results. The effect of hydrogen-transfer additives ($Ph_2CO$, $Al(OiPr)_3$) on the reaction was negligible (Table S-2). Yet, $^1H$ NMR analyses of crude reaction mixtures consistently revealed the presence of benzaldehyde (in the order of 2 mol% or more) also in the absence of such additives, which supports the importance of alcohol dehydrogenation in the process.

The temperature of 250 °C in the microwave experiments is higher than in Fischer's sealed tube experiments (210–220 °C over 12–14 h), in turn the reaction time could be reduced to 1 h. In some of the screening reactions, internal overpressure (> 30 bar) built up that occasionally led to vial ruptures; the pressure is presumably caused by evolution of hydrogen. By working at or below 240 °C, and by using four or less equivalents of base, such incidents were largely prevented. With the unsymmetrical isopropyl-phenyl-pyrrole **5** (*vide infra*) as substrate, a mixture of the monoalkylated regioisomers **6**/**7** in similar amounts emerged (Scheme 3, a).



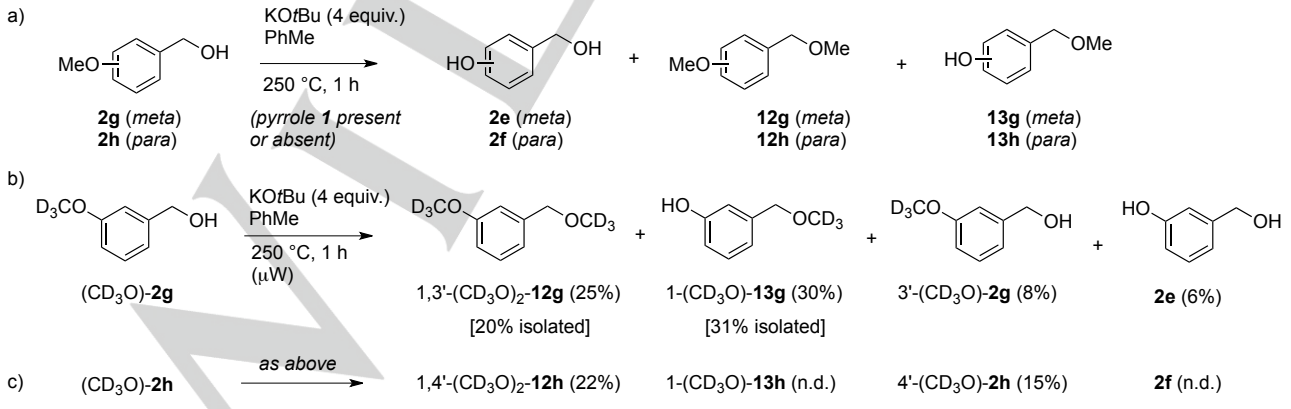

**Scheme 3.** a,b) Alkylation of **5** and **8** in the presence of base; "neat" reactions use BnOH as solvent (2.0 mL per mmol), reactions in toluene use 6.0 equiv. of BnOH. c) Direct alkylation of diester **11**; analytical yield in mol% as determined by qNMR against internal standard.

With 2,4-dimethylpyrrole (**8**), dibenzylation to **10a** was achieved in very short time in neat alcohol, but monoalkylated **9a** was the dominant product in toluene at the hour mark (Scheme 3, b). The higher reaction rate of **8** vs. **1** is in line with the established higher nucleophilicity at the C-2/5 over the C-3/4 position in pyrroles.[22] Those observations support an attack of the pyrrole (or its anion) on an electrophile as a key step. Many alkylated pyrroles including **8** are air-sensitive liquids with a limited shelf life. The standard synthesis of **8** proceeds from the air-stable diester **11** via de-alkoxycarbonylation in strong base.[23] It would be attractive to couple this base-mediated step with a consecutive alkylation, and in fact, **11** is alkylated with **2a** under basic conditions to give **4a** in yields matching those of the reaction starting with **8** (Scheme 3, c). This observation could point to a general strategy for performing HAT-alkylations of electron-rich heterocycles by way of their more stable ester derivatives. The Fischer-type HAT-alkylation of 2,5-dimethylpyrrole (**1**) was shortly tested with substituted benzyl alcohols, and while the alkylation products **3** and **4** were observed, it became evident that optimal results would require individual optimization of the reaction conditions (Scheme 4).




**Scheme 4.** Variation of benzylic alcohols in the base-mediated alkylation of **1**.

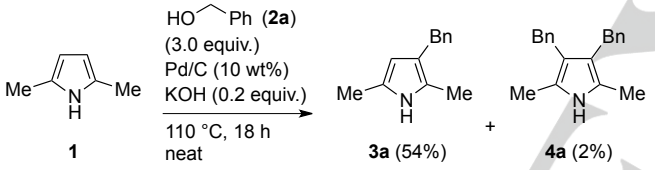
A remarkable observation in attempted alkylations of pyrroles with 3- and 4-methoxybenzyl alcohol (**2g,h**) was the generation of methyl ethers by *O*-methylation of the benzylic alcohol, with the methoxy group from the substrate either left intact (**12**), or dealkylated (**13**). The pyrrole was unaffected in this reaction and could be left out with no change in the result (Scheme 5, a).




**Scheme 5.** a) Initial observation of transmethylations in attempted pyrrole alkylations. b) Base-induced alkyl transfer in deuterium labeled 3-($CD_3O$)-methoxybenzylalcohol (**2g**) at high temperature. c) Base-induced transalkylation of 4-($CD_3O$)-methoxybenzyl alcohol (**2h**).

It was not immediately obvious if this alkyl transfer from an aromatic methyl ether to a benzyl alcohol was due to a direct, $S_N2$-type substitution, or if a HAT-type process involving transfer of a formaldehyde equivalent and hydride might be responsible. Control experiments with deuterium labeled alcohols ($CD_3O$)-**2g** and ($CD_3O$)-**2h** produced a mixture of di- (**12**) and mono-methylated (**13**) methyl ethers in which all methoxy groups fully retained their deuterium without scrambling (Scheme 5b, c). An $S_N2$-transfer by intermolecular attack of alkoxide on the methoxy group of the aryl-ether is most plausible, and while we are not aware of any literature precedent, the high reaction temperature undoubtedly facilitates this $S_N2$-transetherification.

Even if historically and conceptually important, the Hans-Fischer-alkylation of pyrroles is limited in terms of substrate range and by the harshness of reaction conditions, which can lead to unexpected side-reactions such as transalkylation. Our next aim was to realize pyrrole alkylations under milder conditions taking advantage of recent developments in metal-catalyzed HAT-alkylation. Very common, heterogeneous Pd/C-catalysts have been applied for the HAT-alkylation of amines[24] or indole[3d] with alcohols. Application of this catalyst system to the alkylation of dimethylpyrrole **1** with benzyl alcohol are shown in Scheme 6.




**Scheme 6.** Pd/C-catalyzed HAT-alkylation of 2,5-dimethylpyrrole (**1**). Analytical yield in mol-% as determined by qNMR against internal standard.

The reaction proceeds under much milder thermal conditions (110 °C) than the original Hans-Fischer-alkylation. Base additive is still essential, but a substoichiometric quantity is sufficient. KOH gave slightly better results than KO*t*Bu. The reaction was extended to 1-octanol (**2i**) as aliphatic alcohol, which gave 20% of monoalkylated pyrrole (**3i**) at 160 °C. With 2,4-dimethylpyrrole (**8**) and benzyl alcohol (**2a**), a 34% yield of monoalkylated **9a** was obtained (Table S-3).

Finally, we wished to investigate the potential of HAT-alkylation of pyrroles with homogenous catalyst systems based on established ruthenium catalysts, and a few selected iridium pincer complexes (Figure 1).

The iridium *NCP*–pincer complex **14** of Huang *et al* has previously been used in HAT-alkylations of esters at the acidified α-C–H-position,[25] whereas iridacycles based on bis(phosphanylamino)triazine ligands **L**[26] (Figure 1) were introduced by Kempe *et al* for dehydrogenative condensation syntheses of pyrroles or pyrimidines,[27] whereas their cobalt- or iron-complexes have shown activity in HAT-alkylations of amines with alcohols.[28]

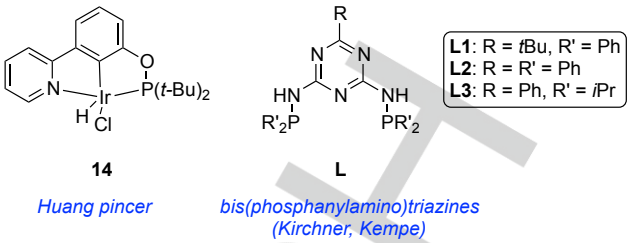
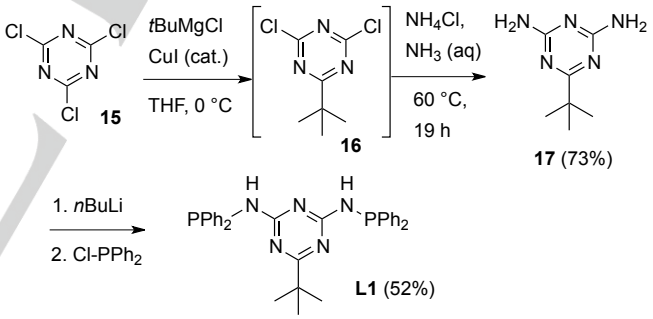



**Figure 1.** Structures of the Huang Ir-NCP pincer complex (**14**) and of Kirchner' bis(phosphanylamino)triazine ligands (**L**) as precursors for Kempe's Ir-PNP pincer catalysts.

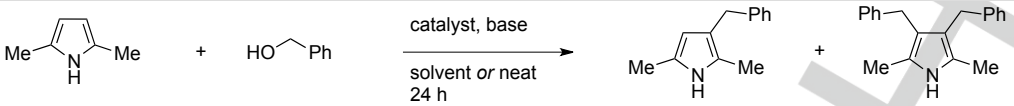
Ligands **L** have the advantage of a highly modular construction principle based on on a combination of 6-substitued 1,3,5-triazine-2,4-diamines and two equivalents of dialkylchloro-phosphane ($R_2PCl$; R = *i*Pr, *t*Bu). For the present work we extended the ligand range to 6-*tert*-butyl substituted derivative **L1**, whose synthesis takes advantage of our selective copper-catalyzed *tert*-alkylation of multiply halogenated azines.[29] Cyanuric chloride (**15**) was coupled with one equivalent of *t*BuMgCl to give **16**, which was aminated without isolation in the same pot by adding ammonia and ammonium chloride for solubilization of magnesium salts (Scheme 7). The new ligand **L1** was obtained by phosphanylation under basic conditions.




**Scheme 7.** Synthesis of a new *PNP*-pincer ligand (**L1**) based on selective copper-catalyzed *tert*-alkylation of cyanuric chloride.

Reaction screening started with the system Ru–DPEphos–$K_3PO_4$, which had previously been successful in HAT-alkylation of indoles.[3d] The catalyst system also showed activity for pyrrole alkylation, but a stronger base was necessary for achieving conversion at 110 °C (Table 2, entries 1 *vs.* 2). Iridium pincer complex **14** did not show satisfactory activity in pyrrole alkylation, and mono- *vs* dialkylation selectivity was low (entries 3, 4). Best results were eventually obtained with Kempe type *PNP*-iridium-pincers, which were formed *in situ* from suitable iridium precursors and bis(phosphinylamino)triazine ligands **L1**–**L3** (Figure 1) by allowing both components to pre-complex at 50 °C for 1 h.

**Table 2.** Catalyst screening for the HAT-alkylation of 2,5-dimethylpyrrole (**1**).[a]



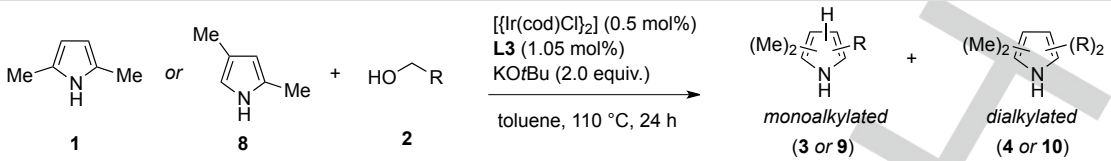

**1** **2a** **3a** **4a**

| Entry | Precursor (mol%) | Ligand (mol%) | Base (equiv.) | BnOH [equiv.] | Solvent | T [°C] | **3a** [%][b] | **4a** [%][b] |
|---|---|---|---|---|---|---|---|---|
| 1 | $RuCl_2(PPh_3)_3$ (1.25) | DPE-Phos (1.25) | $K_3PO_4$ (3.0) | 5 | neat | 165 | 40 | 12 |
| 2 | $[Ru(p\text{-cym})Cl_2]_2$ (2.5) | DPE-Phos (5.0) | KO*t*Bu (5.0) | 10 | toluene | 110 | 53 | 2 |
| 3 | **14** (2.0) | - | - | 3 | neat | 150 | 23 | 27 |
| 4 | **14** (2.0) | - | KO*t*Bu (0.2) | 3 | neat | 150 | 26 | 9 |
| 5[c,d] | [{IrOMe(cod)}$_2$] (1.5) | **L3** (3.0) | KO*t*Bu (2.0) | 10 | dioxane | 105 | 26 | 1 |
| 6[c] | [{IrOMe(cod)}$_2$] (2.0) | **L1** (4.2) | KO*t*Bu (2.0) | 10 | toluene | 110 | 57 | 3 |
| 7[c] | [{Ir(cod)Cl}$_2$] (2.0) | **L1** (4.2) | KO*t*Bu (2.0) | 10 | toluene | 110 | 64 | 6 |
| 8[c] | [{Ir(cod)Cl}$_2$] (2.0) | **L3** (4.2) | KO*t*Bu (2.0) | 10 | toluene | 110 | 70 | 6 |
| 9[c] | [{Ir(cod)Cl}$_2$] (2.0) | **L2** (4.2) | KO*t*Bu (2.0) | 10 | toluene | 110 | 70 | 3 |
| 10[c] | [{Ir(cod)Cl}$_2$] (2.0) | **L2** (4.2) | $K_3PO_4$ (2.0) | 10 | toluene | 110 | 44 | 1 |
| 11[c] | [{Ir(cod)Cl}$_2$] (1.0) | **L2** (2.1) | KO*t*Bu (2.0) | 10 | toluene | 110 | 62 | 3 |
| 12[c] | [{Ir(cod)Cl}$_2$] (1.0) | **L3** (2.1) | KO*t*Bu (2.0) | 10 | toluene | 110 | 71 | 7 |
| 13[c,d] | [{Ir(cod)Cl}$_2$] (0.5) | **L3** (1.05) | KO*t*Bu (2.0) | 10 | toluene | 110 | 70 (52) | 4 |
| 14[c,d] | [{Ir(cod)Cl}$_2$] (0.5) | **L3** (1.05) | KO*t*Bu (2.0) | 5 | toluene | 110 | 51 | 5 |
| 15[c,d] | [{Ir(cod)Cl}$_2$] (0.5) | **L3** (1.05) | KO*t*Bu (1.0) | 10 | toluene | 110 | 61 | 2 |
| 16[d] | [{Ir(cod)Cl}$_2$] (0.5) | **-** | KO*t*Bu (2.0) | 10 | toluene | 110 | 34 | 3 |

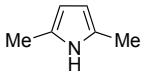
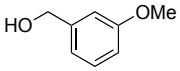
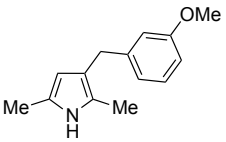
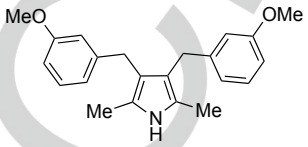
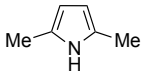
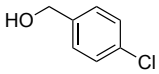
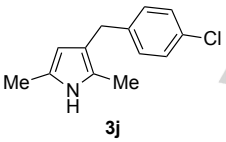
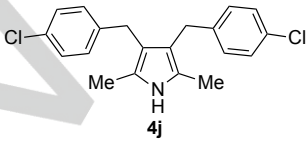
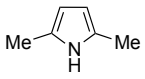
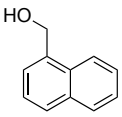
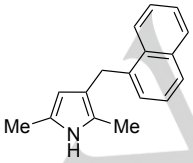
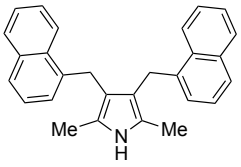
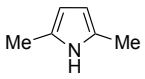
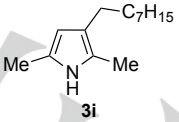
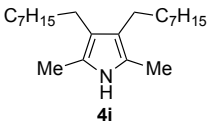
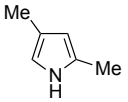
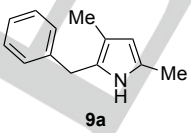
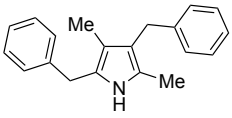
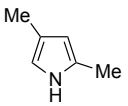
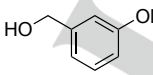
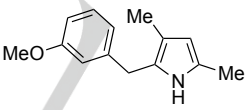
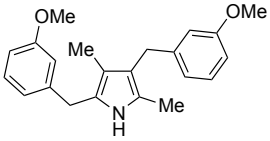
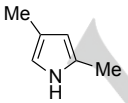
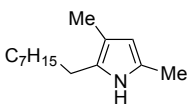
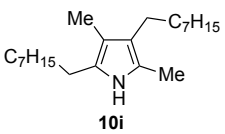
[a] All reactions were performed with 1.0 mmol pyrrole. [b] Yields were determined by qNMR against 1,1,2,2-tetrachloroethane as internal standard. Isolated yields are given in parenthesis. [c] Precomplexation of Ir-precursor and ligand for 1 h at 50 °C in the corresponding solvent. [d] 1.5 mmol pyrrole.

Up to 70% of **3a** was obtained with such a catalyst, with high selectivity over dialkylation (entries 5–16). **L3** appeared to be the most active ligand at lower catalyst loadings. Metal loading could be lowered to 1 mol% of iridium with no loss of activity (entry 13). A sufficient excess of alcohol was required for achieving high conversion (entry 14 *vs* 13). The reaction still proceeds in the absence of ligand, but the yield was lower (entry 16). In comparison to the base-catalyzed Hans-Fischer-alkylation, the iridium-catalyzed process is active at much lower temperature (110 *vs* 240 °C). The best conditions (entry 13) were also reproduced by mixing all reaction components including the metal precursor and ligand **L3** at the outset of the reaction to obtain the products in essentially the same yield (70% **3a** + 6% **4a**), with no need for a precomplexation phase. The optimal catalyst system from the screening successfully realized the alkylation of pyrroles **1** and **8** with some substituted benzylic alcohols (**2**) in similar yields compared to **2a** (Table 3, entries 1, 2).

**Table 3.** Variation of the alcohol in the catalytic HAT-alkylation of pyrroles.[a]




1 8 2

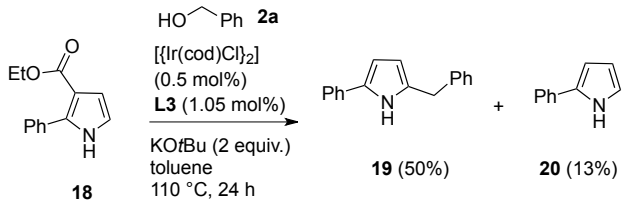
| Entry | Pyrrole | Alcohol | Monoalkylation product | Yield[b] | Dialkylation product | Yield[b] |
|---|---|---|---|---|---|---|
| 1 |  **1** |  **2g** |  **3g** | 68 |  **4g** | 4 |
| 2 |  **1** |  **2j** |  **3j** | 69 |  **4j** | 3 |
| 3 |  **1** |  **2d** |  **3d** | 21 |  **4d** | 3 |
| 4 |  **1** | *n*OctOH (**2i**) |  **3i** | 43 |  **4i** | 0 |
| 5 |  **8** | BnOH (**2a**) |  **9a** | 49 |  **10a** | 20 |
| 6 |  **8** |  **2g** |  **9g** | 55 |  **10g** | 12 |
| 7 |  **8** | *n*OctOH (**2i**) |  **9i** | 63 |  **10i** | 10 |

[a] All reactions were performed with 1.5 mmol pyrrole. Precomplexation of [{Ir(cod)Cl}$_2$] and **L3** in toluene for 1 h at 50 °C. [b] Yields were determined by qNMR against 1,1,2,2-tetrachloroethane as internal standard.

The somewhat bulky 1-naphthylmethanol (**2d**) gave a low yield of monosubstituted product **3d** (entry 3). This can be attributed to steric hindrance, which may be pronounced in the presumed intermediary arylidene-azafulvene (*vide infra*). With an aliphatic alcohol, the conversion was lower (entry 4). Pyrrole **8** gave mixtures of mono- (**9**) and dialkylation (**10**) products under the

catalytic alkylation conditions, with monoalkylation being favored. This underlines the higher reactivity of this substrate as a result of having available a free α-position (entries 5–7). Consequently the C-5-position is always alkylated first, whereas products of C-3-monoalkylation have not been observed. Reactions with secondary alcohols including isopropanol or 1-phenylethanol were not successful.

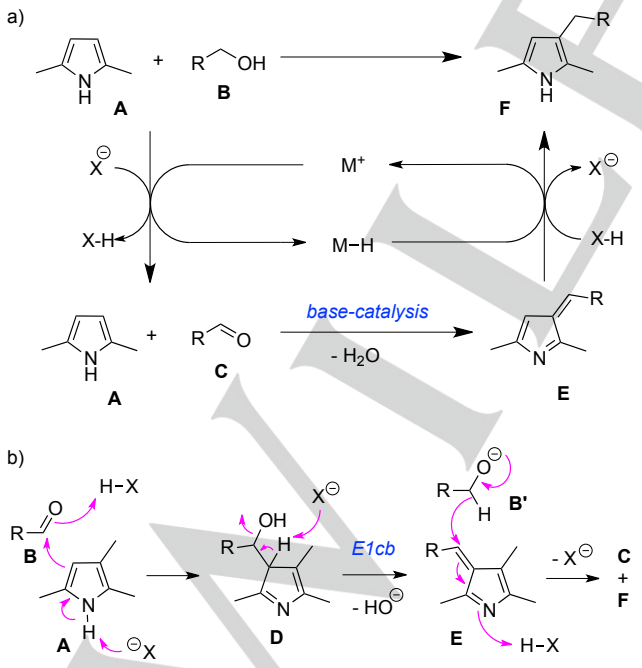
As in case of the base-catalyzed pyrrole alkylation, the iridium-pincer-catalyzed reaction could be performed with pyrrole carboxylic esters[30] as starting material, which undergo consecutive de-alkoxycarbonylation and alkylation (Scheme 8).




**Scheme 8.** Iridium-pincer complex and base catalyzed consecutive de-alkoxycarbonylation/HAT-alkylation of a pyrrole ester. Isolated yield is given for **19**, qNMR yield for **20**.

The *N*-substituted substrate *N*-phenyl-2,5-dimethylpyrrole was not alkylated by benzyl alcohol under those conditions; neither did it react under the Pd/C–KOH conditions, or under the Hans-Fischer-alkylation conditions with base as exclusive catalyst.

We can now propose a mechanistic scheme for this reaction and its variations (Scheme 9, a).




**Scheme 9.** Proposed mechanisms for: a) metal-catalyzed, or; b) base-induced HAT-alkylation of pyrroles with alcohols.

Starting from the general mechanism of HAT-alkylation (cf. Scheme 1) and taking into account the mechanism of base-catalyzed HAT-alkylation of indoles,[10] we may assume that alcohol **B** is deprotonated by a general base (abbreviated $X^-$) to give the alkoxide **B'** (Scheme 9, b), which is oxidized by β-hydride elimination to the metal center (Ir, Ru; via their alkoxides), thereby giving aldehyde **C**. The presence of aldehyde in final reaction mixtures (and thus also during the reaction) was proven by qNMR analysis. Next, electrophilic aldehyde **C** is attacked either by free pyrrole **A** or its *N*-centered anion as nucleophile, with H-X acting as general acid (Scheme 9, b). This step is corroborated by the regioselectivity of the overall reaction, which mirrors the known nucleophilicity pattern in pyrroles. Addition product **D** will easily eliminate water to give azafulvene **E**, which can be reduced to the final, alkylated pyrrole **F** by hydride transfer from the metal hydride. In case of the base-induced Hans-Fischer-alkylation, one may assume that the reduction-step occurs as a conjugate 1,4-hydride transfer from alkoxide **B'** (as in the Cannizarro-reaction,[8] or in hydride transfers from Hantzsch-esters[31]) to azafulvene **E**, with concomitant general acid catalysis by HX, which will usually be alcohol **B** itself (Scheme 8, b). Azafulvene intermediates of pyrroles are not particularly well known in the pure state, but the related 3-benzylidene-3*H*-indole is a stable compound.[32] Furthermore, azafulvenes related to pyrroles are postulated as intermediates in the reduction of acyl- to alkylpyrroles by sodium borohydride.[33]

## Conclusions

In this project, we have explored the possibilities of HAT-alkylations of simple model pyrroles. At the outset, we were inspired by an early report from Hans Fischer, who described pyrrole alkylation by alkali alkoxides in alcohols at elevated temperature (210–220 °C, sealed tube conditions). The mechanism of that reaction had been considered an unsolved problem for many years.[13,19,20] By heating model pyrroles with potassium *tert*-butoxide and benzyl alcohol in a microwave reactor to 240–250 °C, we have been able to reproduce the observations of Hans Fischer in that we obtained a range of alkylated pyrroles. The similarity of the reaction conditions and regioselectivity indicate that the early Hans-Fischer-alkylation is mechanistically closely related to what is currently discussed as "borrowing hydrogen" reaction or HAT-alkylation. In particular, the chemistry is also related to recent work by Yus *et al* on the base-catalyzed HAT-alkylation of indoles.[10] The Hans-Fischer-alkylation of pyrroles requires harsh reaction conditions, which also induce a remarkable $S_N2$-transalkylation of a methyl group from aromatic methyl ethers to primary alkoxides (Scheme 5). Even if the chemoselectivity of the process is thus limited, it was possible to obtain 50–60% of single, pure alkylation products in suitable model reactions. Furthermore, we were able to realize the reaction starting from pyrrole esters rather than free pyrroles as substrates, because cleavage of the alkoxycarbonyl group and *C*-alkylation are both induced by strong base. Considering

that pyrroles tend to be quite unstable and cannot be stored for prolonged time, this approach has practical advantages.

In the second part of this work we have modernized the alkylation chemistry introduced by Hans Fischer in 1912 through application of most recent tools from the field of transition-metal catalyzed HAT-alkylations. The most successful catalyst systems for HAT-alkylation of pyrroles identified in this work are in-situ generated iridium-*P,N,P*-pincer-complexes based on bis(phosphinalymino)triazine ligands, which Kempe *et al* had earlier used in dehydrogenative condensation reactions.[27] We now find that such complexes are suitable HAT-alkylation catalysts which allow to carry out the HAT-alkylation of pyrroles under fairly mild reaction conditions (110 °C, 24 h).

## Experimental Section

**General Remarks:** *Chemicals*: Unless otherwise specified, all reagents and solvents were obtained from commercial suppliers and used without further purification. 2,5-dimethylpyrrole (**1**),[34] 2,4-dimethylpyrrole (**8**),[23b] 2-isopropyl-5-phenylpyrrole (**5**),[35] diethyl 2,4-dimethylpyrrole-3,5-dicarboxylate (**11**)[23a] and ethyl 2-phenylpyrrole-3-carboxylate (**18**)[30] were prepared according to literature procedures. Ir-NCP pincer complex **14** and ligands **L2**, **L3** were prepared according to refs.[35,25a,26]

*Solvents* for water-free reactions were dried by passing through a column of $Al_2O_3$ and then kept over 3 Å molecular sieves under an argon atmosphere.[36] The residual water content in dried solvents was analyzed by coulometric Karl Fischer titration.

*Chromatography*: Column chromatography (CC) was performed on silica gel 60 (35–70 μm particle size), usually as a flash chromatography with 0.2 bar positive air pressure. Thin layer chromatography was performed on glass plates coated with silica gel 60 $F_{254}$ and visualized with UV light (254 nm), molybdenum stain (Mostain)[37] or anisaldehyde stain.[38]

*Microwave reactions*: Reactions with microwave heating were performed in a mono-mode type microwave reactor (Anton Paar Monowave 300) at a fixed target temperature (measured by IR sensor) with adaptive power setting under adiabatic conditions. The reaction time indicated refers to heating at target temperature without heating and cooling phases.

*Analytical data*: NMR spectra were recorded at 300, 400, or 500 MHz ($^1$H) at ambient temperature (19–25 °C). Chemical shift $\delta$ is given in ppm. $^1$H NMR spectra were internally referenced to tetramethylsilane (TMS, $\delta_H$ 0.00) or residual solvent peaks; in $CDCl_3$: $\delta_H$ 7.26; in ($D_6$)-DMSO: $\delta_H$ 2.50. $^{13}$C NMR spectra were referenced to solvent peaks; $CDCl_3$, $\delta_C$ 77.16; ($D_6$)-DMSO, $\delta_C$ 39.52.

*Reaction component analysis by qNMR*: Yield determinations by qNMR were carried out by means of suitable internal standards and appropriate pulse sequences, typically using a pulse repetition delay d1 of ≥20 sec, see ref.[39]

**General procedure 1 for the microwave-assisted, base-catalyzed pyrrole alkylation (GP 1):** Into a microwave glass vessel equipped with a stirring bar (1 cm) were added pyrrole (1.00 mmol), alcohol (2 mL if neat), base and, if indicated, additional solvent (2 mL). The reaction mixture was heated in a microwave reactor using a temperature-driven variable power setting. After the target temperature was reached, it was kept constant for the indicated reaction time. Following cooling to room temperature, a saturated solution of aq. $NH_4Cl$ (and optionally water to dissolve solid residues) was added. The phases were separated and the aqueous phase was extracted with $Et_2O$ (3x). The combined organic phase was washed with water and brine and dried over $MgSO_4$. $Et_2O$ was removed in vacuum (≥500 mbar) and 1,1,2,2-tetrachloroethane (20 μL, 0.191 mmol) was added as internal standard for qNMR.

**General procedure 2 for the Pd/C-catalyzed pyrrole alkylation (GP 2):** A 10 mL Schlenk tube was charged with pyrrole (1.00 mmol), Pd/C (10 wt.-% of catalyst, 5% Pd on carbon), alcohol and base under argon. The tube was closed and the reaction mixture was heated for the indicated time in an oil bath. After cooling to room temperature, the mixture was filtered through celite; the celite was washed with $Et_2O$. The filtrate was evaporated in vacuum (≥500 mbar), and 1,1,2,2-tetrachloroethane (20 μL, 0.191 mmol) was added as internal standard for qNMR.

**General procedure 3 (GP 3) for the homogenously catalyzed pyrrole alkylation without precomplexation (Table 2, entries 1–4+16):** A 10 mL Schlenk tube was charged with 2,5-dimethylpyrrole (**1**), metal complex, ligand, base, alcohol (**2**) and, if indicated, dry toluene (1 mL/mmol) under argon. The tube was closed and the reaction mixture was heated at the specified temperature for 24 h in an aluminum block. After cooling to room temperature, $Et_2O$ and saturated $NH_4Cl$ aq. were added. The phases were separated, the organic phase washed with water and brine and dried over $MgSO_4$. After filtration, $Et_2O$ was removed in vacuum (≥500 mbar), and 1,1,2,2-tetrachloroethane was added as internal standard for qNMR.

**General procedure 4 (GP 4) for the homogenously catalyzed pyrrole alkylation with precomplexation of ligand and metal precursor (Table 2, entries 5–15 and Table 3):** A 10 mL Schlenk tube was charged with iridium-precursor, ligand and dry solvent under argon. The reaction mixture, which immediately turned red, was stirred at 50 °C for 1 h. The oil bath was removed and pyrrole, alcohol, base and additional dry solvent were added. The tube was closed and the mixture was heated at the specified temperature for 24 h in a metal heating block. After cooling to room temperature, $Et_2O$ and a saturated solution of aq. $NH_4Cl$ were added. The phases were separated, the organic phase was washed with water and brine and dried over $MgSO_4$. After filtration, $Et_2O$ was removed in vacuum (≥500 mbar) and 1,1,2,2-tetrachloroethane was added as internal standard for qNMR.

**Deuterium labeling experiments on the base-induced alkyl-transfer**

**Syntheses of deuterated substrates:**

**((3-($D_3$)-Methoxy)phenyl)methanol (($CD_3O$)-2g):** To a solution of 3-hydroxybenzyl alcohol (2.00 g, 16.1 mmol, 1.00 equiv.) in DMF (10 mL) was added powdered potassium carbonate (3.80 g, 27.5 mmol, 1.71 equiv.) and $CD_3I$ (1.25 mL, 20.0 mmol, 1.24 equiv.) under vigorous stirring. The resulting suspension was stirred for 30 h at room temperature. The reaction was quenched by addition of a water/brine (1:1). After extraction with EtOAc (3x), the combined organic phases were washed with water/brine (1:1, 4x) and dried over $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by column chromatography (hexane–EtOAc 3:1) to give 1.93 g (85%) of ($CD_3O$)-**2g** as colorless oil. $R_f$ 0.20 (hexane–EtOAc 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.30–7.24 (m, 1H, Ar-H), 6.96–6.91 (m, 2H, Ar-H), 6.86–6.80 (m, 1H), 4.67 (s, 2H, C$H_2$OH), 1.76 (br. s, 1H, OH). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 159.98, 142.68, 129.73, 119.21, 113.40, 112.38, 65.40, 54.55 (sept, $J_{C\text{-}D}$ = 22 Hz). HRMS (EI): calcd for $C_8H_7D_3O_2^+$: 141.0864, found 141.0860.

**((4-($OCD_3$)-Methoxy)phenyl)methanol (($CD_3O$)-2h):** To a solution of 4-hydroxybenzaldehyde (1.87 g, 15.3 mmol, 1.00 equiv.) in DMF (10 mL), powdered potassium carbonate (3.60 g, 26.0 mmol, 1.70 equiv.) and $CD_3I$ (1.25 mL, 20.0 mmol, 1.31 equiv.) were added under vigorous stirring. The resulting suspension was stirred for 30 h at room temperature. Ethanol (10 mL) was added to the mixture, followed by sodium borohydride (0.30 g, 7.93 mmol, 0.52 equiv.) in portions. The reaction mixture was stirred for 3 h at room temperature until aldehyde was no longer detected by TLC. Ethanol was removed by rotary evaporation and the residue was partitioned between water, EtOAc and brine. The aqueous phase was extracted with EtOAc (2x). The combined organic phases were washed with water/brine (1:1) and dried over $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by column chromatography (hexane–EtOAc 3:1) to give 1.96 g (91%) of ($CD_3O$)-**2h** as colorless oil. $R_f$ 0.17 (hexane–EtOAc 3:1). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.29 (d, $J$ = 7.9 Hz, 2H, Ar-H), 6.89 (d, $J$ = 8.0 Hz, 2H, Ar-H), 4.61 (s, 2H, C$H_2$OH), 1.67 (bs, 1H, OH). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 159.33, 133.24, 128.77, 114.07, 65.15, 54.61 (sept, $J_{C\text{-}D}$ = 22 Hz). HRMS (EI): calcd for $C_8H_7D_3O_2^+$: 141.0864, found 141.0861. Known compound, CAS 14629-71-1.

**Alkyl-transfer experiments:**

***Preparative run with (3-($OCD_3$)-methoxyphenyl)methanol*:** A microwave vial was charged with (3-($OCD_3$)-methoxyphenyl)methanol (($CD_3O$)-**2g**; 706 mg, 5.00 mmol, 1.00 equiv.), potassium *tert*-butoxide (561 mg, 5.00 mmol, 1.00 equiv.) and toluene (2 mL). The reaction mixture was heated in a microwave reactor at 250 °C for 1 h. After cooling to room temperature, a saturated solution of aq. $NH_4Cl$ (5 mL) and EtOAc (20 mL) was added. After separation of the phases, the organic layer was washed with water (5 mL) and brine (5 mL) and dried over $NaSO_4$. The solvent was evaporated and the crude product mixture was purified by column chromatography (hexane–EtOAc 20:1 → 4:1) to afford 1-($CD_3O$)-**13g** (218 mg, 31%) and 1,3'-$(CD_3O)_2$-**12g** (156 mg, 20%) as colorless oils.

*(3-($D_3$)-methoxymethyl)phenol (1-($CD_3O$)-**13g**)*: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.21 (t, $J$ = 7.8 Hz, 1H, Ar-H), 6.88 (d, $J$ = 7.5 Hz, 1H, Ar-H), 6.85–6.82 (m, 1H, Ar-H), 6.76 (dd, $J$ = 8.1, 2.5 Hz, 1H, Ar-H), 5.13 (bs, 1H, OH), 4.43 (s, 2H, C$H_2$OCD$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 156.21, 139.53, 129.79, 120.08, 115.08, 114.81, 74.48, 57.15 (sept, $J_{C\text{-}D}$ = 22 Hz). HRMS (EI): calcd for $C_8H_7D_3O_2^+$: 141.0864, found 141.0862.

*(1-($D_3$)-methoxy)-3-($OCD_3$)-(methoxymethyl))benzene (1,3'-$(CD_3O)_2$-**12g**)*: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.29–7.23 (m, 1H, Ar-H), 6.94–6.87 (m, 2H, Ar-H), 6.83 (dd, $J$ = 7.9, 1.9 Hz, 1H, Ar-H), 4.44 (s, 2H, C$H_2$OCD$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 159.90, 140.01, 129.53, 120.03, 113.50, 112.98, 74.63, 57.26 (sept, $J_{C\text{-}D}$ = 22 Hz), 54.54 (sept, $J_{C\text{-}D}$ = 22 Hz). HRMS (EI): calcd for $C_9H_6D_6O_2^+$: 158.1208, found 158.1203.

**Analytical runs with ($CD_3O$)-2g and ($CD_3O$)-2h:** A microwave vial was charged with deuterium labeled methoxybenzyl alcohol ($CD_3O$)-**2g** or ($CD_3O$)-**2h** (141 mg, 1.00 mmol, 1.00 equiv., 100 mol%), potassium *tert*-butoxide (112 mg, 1.00 mmol, 1.00 equiv.) and toluene (2 mL). The reaction mixture was heated in a microwave reactor at 250 °C for 1 h. After cooling to room temperature, a solution of sat. $NH_4Cl$ aq (3 mL) and EtOAc (15 mL) was added. After separation of the phases, the organic layer was washed with water (5 mL) and brine (5 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuum. The residue was dissolved in $CDCl_3$ and 1,1,2,2-tetrachloroethane (20 µL, 0.191 mmol) was added as internal standard for qNMR.

*$^1$H NMR analysis of reaction mixture from (3-($D_3$)-methoxyphenyl)methanol (($CD_3O$)-**2g**)*: 30 mol% HO-$C_6H_4$-$CH_2OCD_3$ (1-($CD_3O$)-**13g**) ($\delta_H$ 4.39 (s), C$H_2$OCD$_3$), 25 mol% $D_3CO$-$C_6H_4$-$CH_2OCD_3$ (1,3'-$(CD_3O)_2$-**12g**) ($\delta_H$ 4.45 (s), C$H_2$OCD$_3$), 6 mol% HO-$C_6H_4$-$CH_2OH$ (**2e**) ($\delta_H$ 4.56 (s), C$H_2$OH) and 8 mol% starting material (($CD_3O$)-**2g**) ($\delta_H$ 4.63 (s), C$H_2$OH).

*$^1$H NMR analysis of reaction mixture from (4-($D_3$)-methoxyphenyl)methanol (($CD_3O$)-**2h**)*: 22 mol% $D_3CO$-$C_6H_4$-$CH_2OCD_3$ (1,4'-$(CD_3O)_2$-**12h**) ($\delta_H$ 4.39 (s), C$H_2$OCD$_3$) and 15 mol% starting material (($CD_3O$)-**2h**) ($\delta_H$ 4.61 (s), C$H_2$OH).

**Synthesis of Ligand L1**

**6-(*tert*-Butyl)-1,3,5-triazine-2,4-diamine (17):**

*Grignard-reagent*: In a Schlenk flask under argon, Mg turnings (2.67 g, 110 mmol, 1.10 equiv.) were overlaid with dry THF. A crystal of iodine and a small fraction of *tert*-butyl chloride (totally 11.0 mL, 100 mmol, 1.00 equiv.) were added. The mixture was slightly warmed until the color of iodine vanished and the reaction started. The remaining chloride and dry THF (totally 50 mL) were slowly added over 30 min, maintaining a moderate boiling. The reaction mixture was then heated to 65 °C for 1 h. The Grignard-solution was titrated against salicylic aldehyde phenylhydrazone.[40]

*Coupling/amination*:[29] In a Schlenk flask under argon atmosphere, cyanuric chloride (**15**; 7.03 g, 38.1 mmol, 1.00 equiv.) and CuI (362 mg, 1.90 mmol, 0.05 equiv.) were suspended in dry THF (25 mL) and cooled to –20 °C. A solution of *tert*-butyl magnesium chloride (93 mL; 0.43 m in THF, 40.0 mmol, 1.05 equiv.) was added dropwise over 40 min. After warming to 0 °C and stirring for 30 min, the content of the flask was poured into 25% aq. $NH_3$ (400 mL). The mixture was heated to 60 °C and stirred for 19 h. Saturated aq. $NH_4Cl$ was added to dissolve magnesium salts. The mixture was basified with 25% $NH_3$ (aq.) and extracted with EtOAc (3 x). The organic phases were washed with water and brine. After drying over $MgSO_4$ and filtration, evaporation in vacuum gave 6-(*tert*-butyl)-1,3,5-triazine-2,4-diamine (**17**; 4.67 g, 73%) as colorless solid. The compound can be recrystallized from dichloromethane. $R_f$ 0.30 (hexane–EtOAc 1:2). M.p. 168–170 °C (lit.:[41] 169–171 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.02 (br s, 4H, $NH_2$), 1.26 (s, 9H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 186.23, 167.38, 38.56, 28.70. Analysis calcd for $C_7H_{13}N_5$ (167.22): C 50.28, H 7.84, N 41.88; found C 50.01, H 7.80, N 41.91. Known compound, CAS 35841-84-0.

**(6-*tert*-Butyl)-$N^2N^4$-bis(diphenylphosphino)-1,3,5-triazine-2,4-diamine (L1):** Synthesis performed in analogy to refs. [26,27a] A Schlenk flask under argon atmosphere was charged with 6-(*tert*-butyl)-1,3,5-triazine-2,4-diamine (**17**; 500 mg, 2.99 mmol, 1.00 equiv.) and dry THF (20 mL). After cooling to –20 °C (NaCl/ice), *n*-BuLi (4.02 mL, 1.5 m in hexane, 6.13 mmol, 2.05 equiv.) was added dropwise. The resulting white suspension was warmed to r.t. and stirred for 30 min. Chlorodiphenylphosphine (1.10 mL, 5.98 mmol, 2.00 equiv.) was added dropwise at ca. –10 °C and the resulting clear solution was warmed and stirred overnight at r.t. The solvent was removed in vacuum and the slightly yellow, foamy residue was suspended in $CH_2Cl_2$. Filtration removed most of the LiCl-precipitate. The solvent was removed in vacuum and the crude product was purified by column chromatography (in air, hexane–EtOAc 10:1) to afford **L1** (828 mg, 52%) as white, crystalline solid. $R_f$ 0.20 (hexane–EtOAc 10:1). $^1$H NMR (500 MHz, $C_6D_6$): $\delta$ 7.46–7.20 (m, 8H, Ar-H), 7.09–6.89 (m, 12H, Ar-H), 5.62 (br s, 2H, NH), 1.41 (s, 9H, $CH_3$). $^{13}$C NMR (126 MHz, $C_6D_6$): $\delta$ 185.93, 168.23, 139.58 (d, $J$ = 16.1 Hz), 131.59 (d, $J$ = 22.1 Hz), 128.90, 128.39 (d, $J$ = 6.6 Hz),

38.93, 28.65. $^{31}$P NMR (203 MHz, $C_6D_6$): $\delta$ 28.45 (br s, 62%), 25.68 (br s, 38%; tautomers?). HRMS (EI) calcd for $C_{31}H_{31}N_5P_2^+$: 535.2049, found 535.2052.

**Isolated pyrrole alkylation products**

**3-Benzyl-2,5-dimethylpyrrole (3a):** The product was synthesized according to GP 4. A 10 mL Schlenk tube was charged with $[Ir(cod)Cl]_2$ (5.0 mg, 7.5 µmol, 0.5 mol%), ligand **L3** (6.6 mg, 15.8 µmol, 1.05 mol%) and dry toluene (0.2 mL) under argon. The reaction mixture, which immediately turned red, was stirred at 50 °C for 60 min. The oil bath was removed and 2,5-dimethylpyrrole (**1**; 153 µL, 1.50 mmol, 1.00 equiv.), benzyl alcohol (1.55 mL, 15.0 mmol, 10.0 equiv.), potassium *tert*-butoxide (337 mg, 3.00 mmol, 2.00 equiv.) and dry toluene (1.3 mL) were added. The tube was tightly closed and the mixture was heated at 110 °C for 24 h in an aluminium heating block. After cooling to room temperature, $Et_2O$ (20 mL) and sat. aq. $NH_4Cl$ (7 mL) were added. The phases were separated; the organic phase was washed with water (5 mL) and brine (5 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuum and the crude product was purified by Kugelrohr distillation (115 °C, 0.15 mbar) to give **3a** (144 mg, 52%) as white crystalline solid. The compound is not very stable and slowly decomposes, even if stored under argon at 4 °C, under exclusion of light. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.42 (bs, 1H, NH), 7.29–7.24 (m, 2H, Ar-H), 7.23–7.19 (m, 2H, Ar-H), 7.18–7.13 (m, 1H, Ar-H), 5.62 (d, $J$ = 2.7 Hz, 1H, Ar-H), 3.72 (s, 2H, CH2), 2.19 (s, 3H, CH3), 2.17 (s, 3H, CH3). $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ 142.86, 128.55, 128.37, 125.58, 125.24, 122.23, 118.25, 107.30, 32.46, 13.11, 11.20. HRMS (EI): calcd for $C_{13}H_{15}N^+$: 185.1199, found 185.1199.

**2-Benzyl-5-phenylpyrrole (19):** The product was synthesized according to the GP 4. A 10 mL Schlenk tube was charged with $[Ir(cod)Cl]_2$ (5.0 mg, 7.5 µmol, 0.5 mol%), ligand **L3** (6.6 mg, 15.8 µmol, 1.05 mol%) and dry toluene (0.2 mL) under argon. The reaction mixture, which immediately turned red, was stirred at 50 °C for 60 min. The oil bath was removed and 2-phenylpyrrole-3-carboxylate (**18**; 323 mg, 1.50 mmol, 1.00 equiv.), benzyl alcohol (1.55 mL, 15.0 mmol, 10.0 equiv.), potassium *tert*-butoxide (337 mg, 3.00 mmol, 2.00 equiv.) and dry toluene (1.3 mL) were added. The tube was closed and the mixture was heated at 110 °C for 24 h in an aluminium heating block. After cooling to room temperature, $Et_2O$ (20 mL) and a saturated solution of aq. $NH_4Cl$ (7 mL) were added. The phases were separated, the organic one was washed with water (5 mL) and brine (5 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuum and the crude product was purified by column chromatography (hexane–EtOAc = 20:1) to give 176 mg (50%) of **19** as a slightly pink solid. $R_f$ 0.52 (hexane–EtOAc 4:1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.00 (bs, 1H, NH), 7.40–7.20 (m, 9H, Ar-H), 7.17–7.10 (m, 1H, Ar-H), 6.45–6.41 (m, 1H, Ar-H), 6.06–6.02 (m, 1H, Ar-H), 4.01 (s, 2H, $CH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 139.39, 132.93, 132.12, 131.64, 128.92, 128.83, 128.80, 126.69, 125.96, 123.59, 108.76, 106.24, 34.39. Known compound, CAS 905971-72-4.

**Supporting Information:** See for further information on the Hans-Fischer-alkylation of pyrroles with alkali alkoxide (Table S-1), additional screening experiments (Table S-2, S-3), analytical data for alkylated pyrroles detected in reaction mixtures and NMR spectra.

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[20] Treibs (ref. [19]) wrote (p. 41): *„Ein bemerkenswerter Erfolg der ersten Pyrrolarbeiten ist die Alkylierungsreaktion mit Alkoholaten zu höher substituierten, besonders Tetraalkylpyrrolen ... , Sie erfordert scharfe Bedingungen und steht ziemlich ohne Analogien da, ihr Mechanismus hat noch keine Erklärung gefunden." („A remarkable success of [Fischer's] ... initial work on pyrroles is the alkylation reaction with alcoholates that provides more highly substituted, especially tetraalkylpyrroles... It requires harsh conditions and is quite without analogies, its mechanism has not yet found any explanation.")*

[21] While not mentioned in the original reports (ref. [13]), this information was conveyed by Alfred Treibs (ref. [19]), who wrote: *"Die Methode war bei der Bearbeitung der Wolff-Kishner-Reaktion gefunden worden; man ließ sich nicht davon abschrecken, daß 3/4 aller Bombenröhren explodierten."* (*"The [pyrrole alkylation] method had been found during studies of the Wolff-Kishner-reaction; one was not deterred by the fact that three out of four sealed tubes exploded."*)

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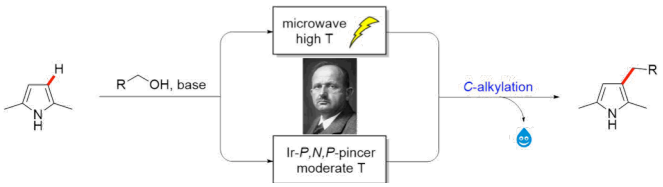


The alkylation of pyrroles with primary alcohols and alkali base at 220 °C was realized by Hans Fischer one hundred years ago. However, this hydrogen autotransfer (*borrowing hydrogen*) alkylation proceeds under much milder conditions in the presence of iridium *P,N,P*-pincer-complex catalysts.

**Hydrogen-Autotransfer-Alkylation**

*Sebastian Koller, Max Blazejak, Lukas Hintermann**

***Page No. – Page No.***

**Catalytic *C*-Alkylation of Pyrroles with Primary Alcohols: Hans Fischer's Alkali, and a New Spin with Iridium *P,N,P*-Pincer Complexes**