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Borrowing Hydrogen in Water and Ionic Liquids: Iridium-Catalyzed Alkylation of Amines with Alcohols

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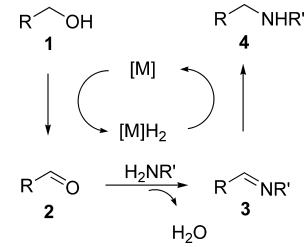
Abstract:

The use of $[Cp^*IrI_2]_2$ as an efficient catalyst for the alkylation of amines by alcohols in either water or ionic liquid is described. Primary amines are converted into secondary amines, and secondary amines into tertiary amines in the absence of base, and the chemistry has been applied to the synthesis of the analgesic fentanyl. The conversion of primary amines into *N*-heterocycles by the reaction with diols is also described, along with the *N*-alkylation of sulfonamides.

Introduction

The alkylation of amines is usually achieved by a substitution reaction with an alkyl halide, although these reactions can lead to overalkylation, and the toxicity of many alkyl halides and related alkylating agents can be problematic.[1] The use of alcohols as direct alkylating agents for amines is appealing since the reaction is atom economical, the alcohol is likely to be less toxic than the corresponding alkyl halide, and the only reaction byproduct is water. Due to the poor electrophilicity of simple alcohols, the direct reaction between amines and alcohols is not readily achieved. The use of the borrowing hydrogen strategy (Scheme 1) provides an alternative method for the dehydrative coupling of amines with alcohols, and proceeds by the temporary removal of hydrogen from a substrate alcohol **1** to provide an intermediate aldehyde **2**. The electrophilic aldehyde readily condenses with an amine, forming imine **3** under the reaction conditions. The catalyst then returns the borrowed hydrogen to the intermediate imine, forming the alkylated amine product **4**. Herein we report the use of the SCRAM catalyst,[2] $[Cp^*IrI_2]_2$, for the alkylation of amines with alcohols using water or ionic liquid as solvent, in the absence of base, where the first comparative study using organic, aqueous, and ionic liquid phases for these reactions is presented. The reaction is applied to the synthesis of the analgesic fentanyl, to the formation of *N*-heterocycles from primary amines, and to the *N*-alkylation of sulfonamides.

Scheme 1. **Alkylation of amines with alcohols using the borrowing hydrogen strategy**



Since the first examples of the alkylation of amines by alcohols using homogeneous catalysts have been published,[3] there have been several ruthenium[4] and iridium[5] catalysts subsequently reported. In particular, Yamaguchi and co-workers have employed $[Cp^*IrCl_2]_2$,[6] for a wide range of amine alkylation reactions. These reactions are typically run in toluene and benefit from the addition of potassium carbonate, which may form the iridium carbonate complex under the reaction conditions.[7] Reactions involving borrowing hydrogen processes have recently been reviewed.[8]

We have recently reported the use of the SCRAM catalyst, $[Cp^*IrI_2]_2$, for the oxidative conversion of aldehydes[9] or amines[10] and *o*-aminophenol into benzoxazoles, as well as the coupling of amines via a borrowing hydrogen pathway involv-

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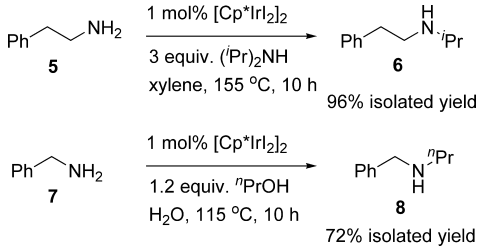
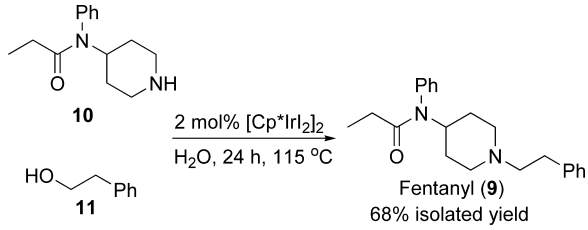
Scheme 2. **Alkylation reactions of amines catalyzed by $[Cp^*IrI_2]_2$**



Scheme 3. **Synthesis of fentanyl using the borrowing hydrogen approach**

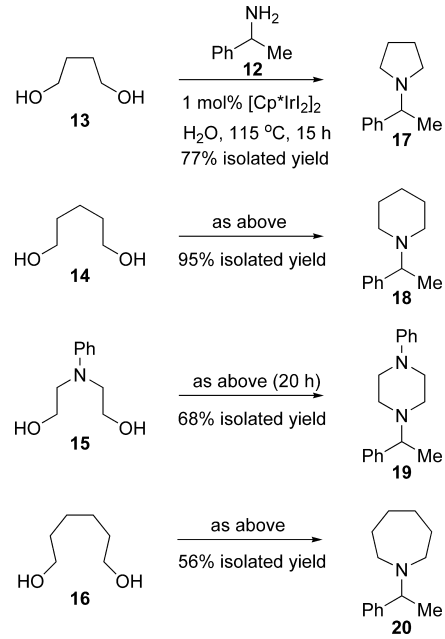


ing temporary imine formation.[11] For example, the reaction of 2-phenylethylamine **5** with diisopropylamine affords the product **6** in excellent isolated yield (Scheme 1). In addition to the coupling of amines, we have discovered that this catalyst is also effective for the *N*-alkylation of amines by alcohols, including the propylation of benzylamine **7** with *n*-propanol to form the secondary amine **8** (Scheme 2).[12] Herein we report further details of this reaction in water and the first examples of using ionic liquids as the medium for borrowing hydrogen methodology. In many cases the correct choice of solvent is a requirement in order to achieve a successful reaction.

Results and Discussion

In order to demonstrate the applicability of the amine alkylation chemistry to the synthesis of pharmaceutically relevant compounds, we chose to examine the synthesis of fentanyl (**9**), which is an analgesic with approximately 100× greater potency than morphine.[13] Commercially available amidopiperidine **10** was reacted with 2-phenylethanol **11** using 2 mol % $[Cp^*IrI_2]_2$ in the absence of base to give fentanyl (**9**) with a reasonable isolated yield (Scheme 3). A higher catalyst loading and reaction time were required in comparison with reactions using unfunctionalized substrates, and it seems plausible that the amidopiperidine starting material and product could act as bidentate ligands to the catalysts, reducing reactivity.

Scheme 4. **Cyclization of amines with diols to form *N*-heterocycles**



Whilst in the fentanyl synthesis we chose to use commercially available piperidine **10**, we wished to examine the synthesis of *N*-heterocycles by the reaction of an amine with a suitable diol. We chose to react 1-phenylethylamine **12** with diols **13**−**16** and were pleased to obtain good conversions and reasonable isolated yields of the corresponding *N*-heterocycles **17**−**20** (Scheme 4). Using water as the solvent, we again observed that additional base was not required in order to activate the catalyst.

The borrowing hydrogen approach has recently been applied to the *N*-alkylation of sulfonamides with alcohols,[14] and we were interested to see whether we could achieve this reaction in water using the $[Cp^*IrI_2]_2$ catalyst. In this case, we did require a base in order to achieve reaction, presumably due to the need to deprotonate the non-nucleophilic sulfonamide in order to generate the intermediate sulfonyl imine. However, we were pleased to see that the reaction in the presence of base was successful for the alkylation of sulfonamides **21** with benzyl alcohol **22** to give the alkylated products **23**−**27** with reasonable isolated yields, except for the formation of the electron-deficient nitro-containing sulfonamide **27** (Scheme 5).

We were interested to examine the effect of using ionic liquids as the reaction medium for borrowing hydrogen reactions, especially since the use of water as a polar solvent had been shown to have a significant effect on these reactions. To the best of our knowledge, there are no previous reports of borrowing hydrogen methodology being performed in ionic liquids. The use of ionic solvents in an industrial context has

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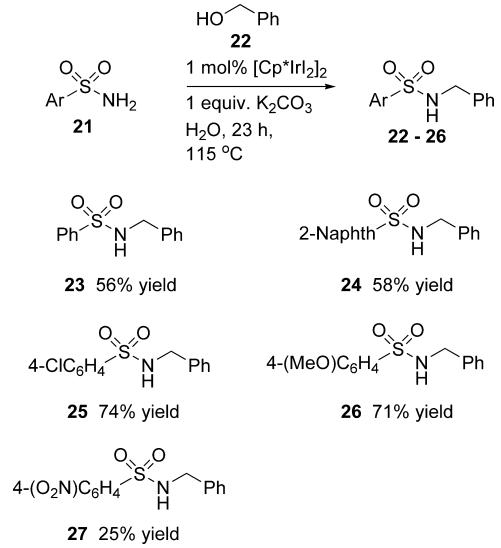
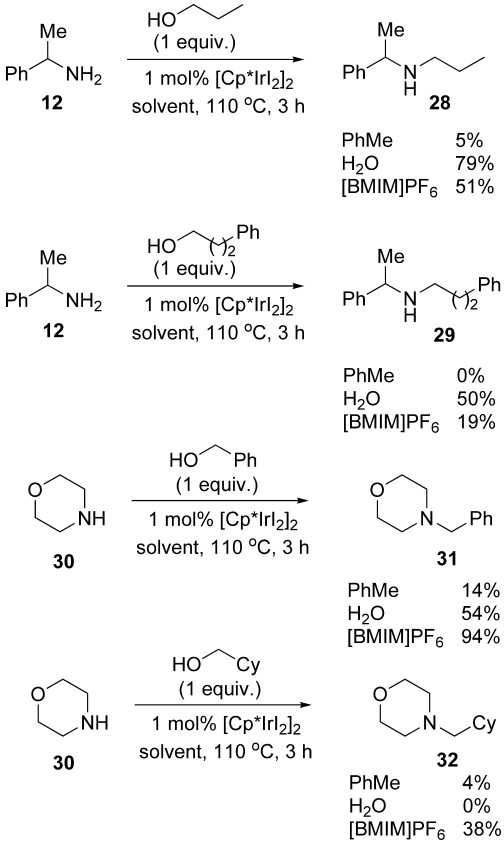
Scheme 5. **N-Alkylation of sulfonamides**



Scheme 6. **Comparison of the use of toluene, water and an ionic liquid for amine alkylation**



recently been reviewed.[15] We chose to run reactions for just 3 h in order to make clear any differences in reactivity when comparing the reaction in water with that in toluene and ionic liquid (Scheme 6). When using the primary amine, 1-phenylethylamine **12**, the alkylation reaction was more successful for the formation of the secondary amine products **28** and **29** in water than in either toluene or the ionic liquid [BMIM]PF_6 (BMIM = 1-butyl-3-methylimidazolium). However, when morpholine **30** was used as the substrate, the formation of

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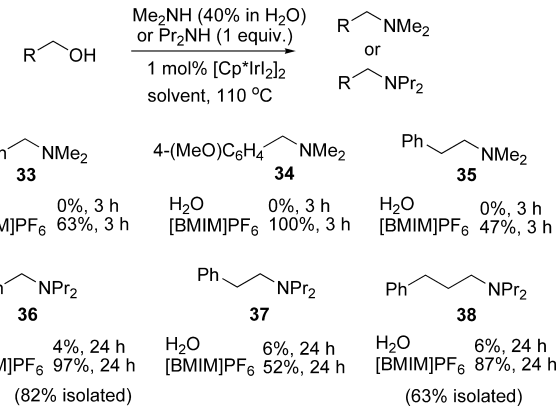
Scheme 7. **Beneficial effect of using an ionic liquid for tertiary amine formation**



tertiary amine products **31** and **32** was greater in the ionic liquid. When *N*-benzylmorpholine **31** was formed in the ionic liquid, 94% conversion was observed and the product isolated in 85% yield. In all cases, the correct choice of solvent was important to obtain good conversion, and the use of toluene as solvent afforded low conversions. We examined alternative ionic liquids as solvents by variation of the counterion, and there was a limited effect on conversion into *N*-benzylmorpholine **31**, with [BMIM]PF_6 giving 94% conversion compared with [BMIM]BF_4 94%, [BMIM]SbF_6 89%, [BMIM]OTf 94%, and [BMIM]Cl 86%. The use of [BDMIM]BF_4 (BDMIM = 1-butyl-2,3-dimethylimidazolium), which contains an additional 2-methyl substituent, led to a 93% conversion. In this latter case, it is not possible for the ionic liquid to become deprotonated to form an *N*-heterocyclic carbene, hence catalyst activation by the formation of an *N*-heterocyclic carbene complex is not a requirement for catalyst reactivity.

Intrigued by the enhanced reactivity that was observed for the formation of tertiary amines, we considered the preparation of acyclic tertiary amines in ionic liquid. After a short reaction time of 3 h, the reaction of dimethylamine with alcohols in water did not lead to the formation of products **33**−**35**. However, using the ionic liquid [BMIM]PF_6 reasonable conversions were achieved, even though the amine was used as a 40% solution in water. In the case of the reaction of dimethylamine with *p*-methoxybenzyl alcohol, complete conversion into tertiary amine **34** was observed in 3 h. In the reactions with di-*n*-propylamine, we allowed the reactions to run for 24 h, where only small amounts of products **36**−**38** were observed when the reactions were run in water, but again, the reactions were much more efficient when performed in [BMIM]PF_6.

These observations suggest that for the formation of a secondary amine from a primary amine, water is slightly preferred as a solvent over the ionic liquid. However, for formation of more hindered tertiary amines, there is a strong preference for the reaction to be performed in ionic liquid (Scheme 7). The mechanism involved in tertiary amine synthesis must proceed via the reduction of an intermediate iminium species, certainly in cases where enamine formation is not possible. It seems unlikely that the iminium would be coordinated to the metal in this case. However, in the synthesis of secondary amines the reaction is likely to proceed via the reduction of an imine, which is more likely to be coordinated

to the metal. We therefore assume that the ionic liquid favors the iminium reduction step, although it is not clear why this is the case. Since variation of the counterion of the ionic liquid had a negligible effect on reactivity, it does not appear to be important that a cationic iridium complex needs to be formed, and we therefore speculate that it is the highly polar environment which encourages iminium reduction.

Conclusion

In summary, we have demonstrated that $[Cp^*IrI_2]_2$ is an effective catalyst for the alkylation of amines with alcohols in the absence of base when the reactions are run in polar media. Sulfonamides are also *N*-alkylated with this catalyst, although base is required in these reactions. The first examples of the use of ionic liquid as solvent for borrowing hydrogen methodology are reported and found to be especially beneficial for the synthesis of tertiary amines.

Experimental Section

Procedure for the Alkylation of 1-Phenylethanamine with 1,4-Butanediol. To an oven-dried, nitrogen-purged carousel tube containing $[IrCp^*I_2]_2$ (11.7 mg, 0.01 mmol) were added the 1,4-butanediol (1 mmol, 87 μL) and 1-phenylethanamine (1 mmol, 127 μL) followed by deionised and degassed water (2 mL). The reaction mixture was then heated to 115 °C at reflux for 15 h. After cooling, the crude mixture was extracted three times with ethyl acetate and dried over magnesium sulfate, and the solvent was removed under vacuum. The resulting residue was purified by flash chromatography eluting with (EtOAc/hexane, 1:10) to give 1-(1-phenylethyl)pyrrolidine **17**[14a] as a colourless oil (135 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.13 (m, 5H), 3.13 (q, J = 6.6 Hz, 1H), 2.52−2.47 (m, 2H), 2.33−2.30 (m, 2H), 1.71−1.69 (m, 4H), 1.35 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 128.3, 128.2, 127.2, 126.8, 65.9, 52.9, 23.4, 23.1; HRMS calcd for $C_{12}H_{17}NH^+$: 176.1439; Found: 176.1435.

Representative Procedure for the Alkylation of Sulfonamides with Benzyl Alcohol. To an oven-dried, nitrogen-purged carousel tube containing $[IrCp^*I_2]_2$ (11.7 mg, 0.01 mmol) and K_2CO_3 (138 mg, 1 equiv) were added the representative sulfonamide (1 mmol) and benzyl alcohol (1.2 mmol, 125 μL) followed by the deionised and degassed water (2 mL). The reaction mixture was then heated to 115 °C at reflux for 20−23 h, depending on the sulfonamide used. After the required time, the crude mixture was extracted three times with ethyl acetate and dried over magnesium sulfate, and the solvent was removed under vacuum. The resulting residue was purified by column chromatography to give the desired product.

Representative Procedure for the Reaction of Alcohol with $HNMe_2$ in Ionic Liquid. $[Cp^*IrI_2]_2$ (11.6 mg, 0.01 mmol) was placed in an oven-dried carousel tube and placed under an inert atmosphere of nitrogen. $[BMIM]PF_6$ (0.5 mL) was added followed by the alcohol (1 mmol) and dimethylamine (40% solution in H_2O, 1.2 mmol, 0.15 mL). The tube was then heated at 115 °C for 3 h before cooling to room temperature. Ethyl actetate was added and the crude extracted three times with diethylether. The combined organics were dried with $MgSO_4$ and concentrated under reduced pressure. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

Acknowledgment

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Supporting Information Available

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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