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Graphical Abstract

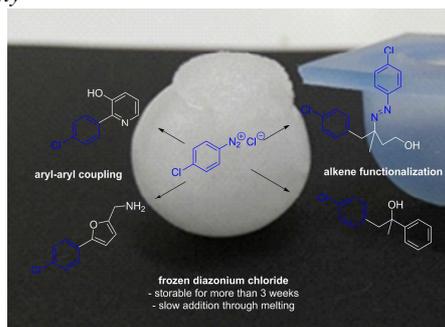
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ABSTRACT

Frozen aryldiazonium chlorides have been investigated in radical alkene and arene functionalizations. Through freezing at -84°C , aryldiazonium chlorides, which otherwise show **significant** decomposition in aqueous solution after several hours at room temperature, can be stored for at least 20 days. In addition, the slow melting of aryldiazonium-containing ice cubes can serve as an alternative to syringe pumps that are commonly used if a controlled addition of the diazonium salt to the reaction mixture is required.

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1. Introduction

Aryldiazonium salts are versatile starting materials for a broad range of organic transformations, which can roughly be divided into three major subgroups.¹ The first group, namely ionic reactions, comprises azo couplings and triazene formations, the Balz-Schiemann and the Japp-Klingemann reaction.² Radical reactions of diazonium salts, representing the second subgroup, include Gomberg-Bachmann- and Pschorr-type aryl-aryl couplings, Meerwein-type alkene functionalizations, Sandmeyer reactions and hydrogen atom transfer reactions, and several others.³ In addition, aryldiazonium salts have been successfully employed in palladium-catalyzed cross-couplings as well as in closely related transition-metal mediated reactions, thereby constituting the third subgroup.⁴ One major drawback that is however commonly associated with aryldiazonium salts is their insufficient stability and the related risk of uncontrolled reactions, even including explosions.⁵ For this reason, large scale reactions and storage should generally be conducted with suitable precautions.⁶ In the overall context, aryldiazonium tetrafluoroborates probably represent the most useful type of salt, as a comparably convenient synthesis is then combined with a long storage life for most substitution patterns, given that the diazonium salt was previously prepared in sufficiently high purity.⁷

Our particular interest in the stability of aromatic diazonium salts arose from the observation that aqueous aryldiazonium chlorides performed better in a number of radical reactions than their related storable tetrafluoroborates.⁸ A plausible explanation for this trend is the fact that an organic co-solvent is usually added so that the tetrafluoroborates can be added to the reaction mixture dropwise by syringe pump. In contrast to purely aqueous

solutions, in which most diazonium chlorides can be obtained, the presence of organic co-solvents such as acetonitrile or dimethylsulfoxide can facilitate undesired hydrogen abstraction by aryl radicals.^{3a} Regarding the overall context, slow addition of the diazonium salt by syringe pump is a common measure to keep the stationary diazonium concentration low. In this way, undesired homo-coupling reactions, particularly the attack of aryl radicals onto unconverted diazonium ions, can effectively be suppressed.^{8a}

Against this general background, it was an interesting question whether the durability of aqueous aryldiazonium chlorides could be increased through freezing.⁹ In this way, the intended radical reactions could be performed with lower amounts of organic co-solvents and the slow melting of the frozen diazonium salts might even render the use of a syringe pump unnecessary.¹⁰ In this article, we now present first results on the use of a frozen aryldiazonium chloride in radical alkene and arene functionalizations.

2. Results and discussion

Initial experiments with silicone ice moulds showed that such devices are suitable for the intended experiments as these moulds allow freezing of the diazonium chloride solution as well as simple removal of the resulting ice spheres and or ice cubes from the mould. An ice sphere (S) and an ice cuboid (C) prepared in this way are shown, after removal from the respective silicone moulds, in Figure 1. The sphere (S) and the cuboid (C) both contain 1.0 mmol of 4-chlorophenyldiazonium chloride in dilute hydrochloric acid. The diameter of the sphere (S) was approximately 17 mm, corresponding to a total volume of ca. 2.5 mL and a concentration of the frozen diazonium chloride of 0.4

M. The ice cuboid (C) was obtained from a more dilute aqueous solution of 4-chlorophenyl-diazonium chloride (0.17 M), which resulted in a total volume of ca. 7.0 mL and an approximate cuboid size of 20×20×18 mm.

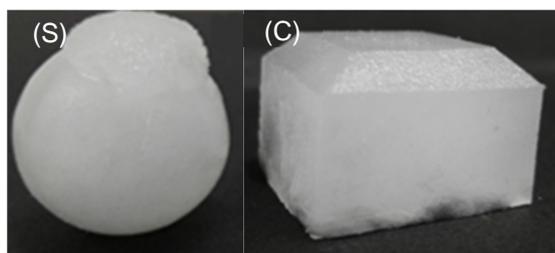


Figure 1. Ice sphere (S) (Ø ca. 17 mm, 2.5 mL) and ice cuboid (C) (ca. 20×20×18 mm, 7 mL).

Further preliminary experiments revealed that freezing of the diazonium chloride solutions could not be achieved at -21°C or -30°C , even after several days. Under these conditions, freezing occurred only partially, and a highly concentrated diazonium salt solutions remained as supernatant above a frozen portion. Complete and fast freezing was however possible for the sphere (S) and the cuboid (C) at -84°C over a time of three hours.

To study the applicability of ice spheres (S) and cuboids (C) in radical arylation reactions, a previously developed base-induced carboamination reaction¹¹ was chosen as a first example. In the original work, dropwise addition of freshly prepared aqueous 4-chlorophenyldiazonium chloride (1) to a mixture of 3-methyl-3-buten-1-ol (2) and sodium carbonate in aqueous acetonitrile at 50°C had provided the carboamination product 3 in a maximum yield of 62%. This reaction was now modified in the way that the diazonium chloride 1 was added as an ice sphere (S) or ice cuboid (C) to the reaction mixture, either directly or via slow melting in a glass funnel placed above the round-bottom flask used as reaction vessel. Note that the ice sphere (S) had the same size and shape as shown in Figure 1, but the ice cuboid (C) had a decreased thickness so that its size of 20×20×6 mm amounted to a volume of 2.5 mL.

Table 1. Comparison of ice shape and addition method in the base-induced radical carboamination of 3-methyl-3-buten-1-ol (2).

entry	ice shape ^a	addition method ^b	melting time [s]	yield [%]
1	(S)	direct	25	55
2	(S)	via funnel	600	42
3	(C)	direct	23	54
4	(C)	via funnel	660	40

^aIce spheres and cuboids (each 2.5 mL) used after freezing for at least 3 h at -84°C . ^bSee experimental section for details.

The results summarized in Table 1 indicate that slow melting in the funnel, resulting in addition times in the range of 600 to 660 seconds (entries 2 and 4), does provide lower yields than fast melting upon direct addition of ice sphere or ice cuboid to the reaction mixture (entries 1 and 3). During direct addition (entries 1 and 3), the temperature of the reaction mixture dropped by 6°C , but reached 50°C again after 5 minutes. No significant difference was observed between the two ice shapes, as shown by

the comparison of the entry pairs 1 and 3, and 2 and 4. On the basis of these results, the direct addition of the frozen diazonium chloride to the reaction mixture was maintained for the next study, but the melting time in the solution was increased through the use of a larger ice cuboid containing the diazonium salt in a more diluted form. The results obtained from the related series of experiments are summarized in Table 2.

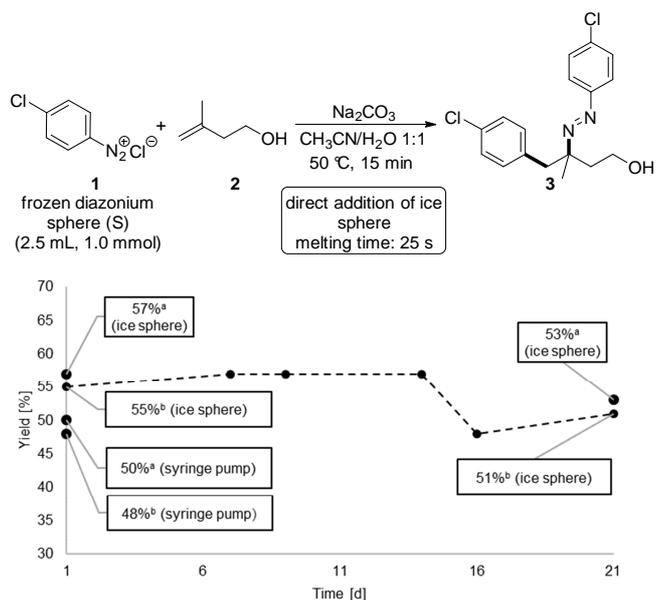
Table 2. Direct addition of ice cuboids to the reaction mixture: effect of dilution and prolonged melting time.

entry	volume of ice cuboid ^{a,b} [mL]	concentration of 1 in ice cuboid [mol/L]	melting time [s]	yield [%]
1	2.5	0.40	23	55
2	3.5	0.29	70	42
3	4.0	0.25	100	43
4	4.5	0.22	201	38
5	5.0	0.20	270	37
6	7.0	0.14	403	34

^aIce cuboids (2.5 – 7.0 mL) used after freezing for at least 3 h at -84°C .

^bSee experimental section for details.

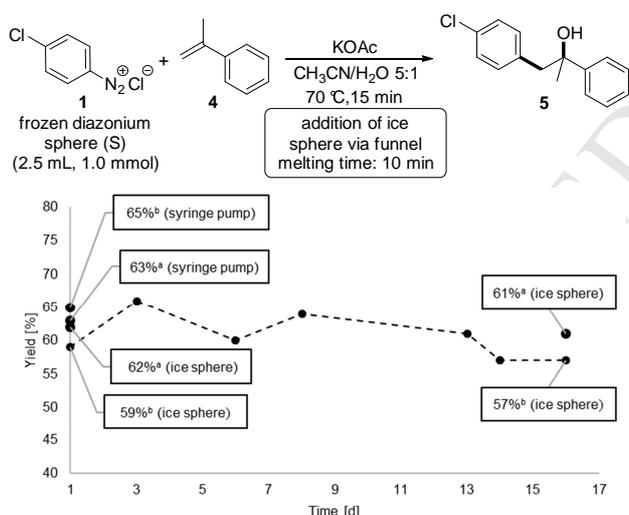
Again, prolonged melting times (entries 2-6) did not lead to improved results, although the longest melting periods of 270 s (4 min 30 sec) and 403 s (6 min 43 s) (entries 5 and 6) were comparable to the original addition of diazonium salt 1 to the reaction mixture by syringe pump over 5 minutes.¹¹ A plausible explanation for the negative effect of increased cuboid size is the temperature impact, which is now apparently too strong, so that the cooling of the reaction mixture becomes too intense. Note that the size and shape of the largest ice cuboid used in entry 6 (Table 2) is exactly identical to the cuboid shown in Figure 1. On this basis, we evaluated the stability of the frozen diazonium ice spheres over time. For this purpose, the previously studied carboamination reaction (Tables 1 and 2) was repeated with ice spheres (Figure 1, (S)) stored in the freezer at -84°C for up to 21 days. The related results are summarized in Scheme 1.



Scheme 1. Base-induced radical carboamination conducted with ice sphere (2.5 mL, 0.4 M, 1.0 mmol) frozen at -84°C for at least 3 h up to 21 d. ^aYield determined after column chromatography. ^bYield determined by $^1\text{H-NMR}$ using dimethyl terephthalate as internal standard.

The reactions conducted on the first day revealed that the addition of the diazonium salt **1** to the reaction mixture in the form of an ice sphere (S) can even be superior to the established addition as an aqueous solution by syringe pump. These two carboamination reactions were carried out using the same diazonium chloride solution, in one case directly after preparation (syringe pump) and in the other case after freezing for 3 h at -84°C via addition of an ice sphere. The fact the yield of the syringe pump experiment (48%/50%) did not reach the previously reported value of 62%¹¹ is most probably due to different batches of chemicals or slight variations in the preparation of the diazonium salt. Evaluating the results of the consecutive experiments conducted on days 7, 9, 14, 16 and 21, a good stability of the frozen diazonium chloride can be assumed.

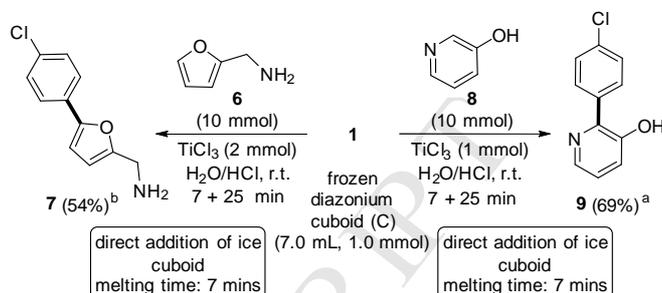
To further explore the suitability of the frozen diazonium chloride **1** for radical alkene functionalizations, a recently developed carbohydroxylation method was investigated.¹² For this transformation, preliminary experiments showed that an addition of the frozen diazonium ice sphere (Figure 1, (S)) to the reaction mixture by slow melting in a funnel is superior to direct addition to the reaction mixture. This effect is contrary to what was observed for the carboamination (Table 1), and could be due to a higher sensitivity of the carbohydroxylation reaction towards a drop of the reaction temperature. The results of a series of experiments with diazonium chloride **1** and α -methylstyrene (**4**) are summarized in Scheme 2.



Scheme 2. Carbohydroxylation conducted with ice sphere (2.5 mL, 0.4 M, 1.0 mmol) frozen at -84°C for at least 3 h up to 16 d. ^aYield determined after column chromatography. ^bYield determined by $^1\text{H-NMR}$ using dimethyl terephthalate as internal standard.

In the case of the carbohydroxylation, the comparison of direct addition by syringe pump or, after freezing, as ice sphere on day 1 gave minimally improved results compared with the classical syringe pump method. Again, the same diazonium chloride solution was used for these two experiments, as well as for the later stability evaluation, to allow unambiguous conclusions. As evidenced by the reactions carried out on days 3, 6, 8, 13, 14 and 16, the diazonium chloride **1** again displayed a good stability at -84°C , and comparable yields were obtained for alcohol **5** over that period of time.

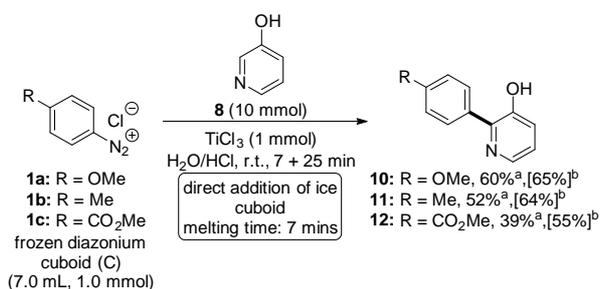
In the next step, the frozen diazonium chloride **1** was applied for two radical aryl-aryl coupling reactions (Scheme 3).^{13,14} As these reactions are typically carried out at room temperature or below, we reasoned that the temperature impact of direct addition should not cause difficulties. Moreover, the more diluted ice cuboid (Figure 1, (C)) was chosen, since the diazonium chloride **1** is, when using a syringe pump, typically added over a time of 10 to 15 minutes.



Scheme 3. Biaryl synthesis using frozen diazonium chloride cuboids. ^aYield determined after column chromatography. ^bYield determined by $^1\text{H-NMR}$ using dimethyl terephthalate as internal standard.

After a few experiments aimed at optimization (see Supporting Information), the heterobiaryls **7** and **9** could be prepared from furfurylamine (**6**) or 3-hydroxypyridine (**8**) in reasonable yields using titanium(III) chloride in acidic solution. In the case of 2-arylpyridine **9**, the isolated yield of 69% compares well with the previously achieved result under syringe pump addition (74%).¹⁴ In contrast to that, the synthesis of the arylfurfurylamine **7** led to a lower yield of 54% compared to 74% by syringe pump addition,¹³ which points to a temperature effect and a higher sensitivity of this particular arylation reaction towards cooling.

Finally, the radical arylation of 3-hydroxypyridine (**8**) was repeated under variation of the substituent on the diazonium salt (Scheme 4). Diazonium salts bearing either a strongly electron-donating (**1a**, R = OMe), a more or less neutral (**1b**, R = Me) or a strongly electron-withdrawing (**1c**, R = CO₂Me) substituent were included in this study. A comparison of the results with those previously obtained under syringe pump addition reveals that the donor-substituted diazonium salt **1a** is best suited for the addition as an ice cuboid in titanium(III)-mediated radical arylations. The acceptor-substituted salt **1c**, on the other hand, led to the lowest yield and also to the largest difference in yield compared to the traditional addition by syringe pump.¹⁴



Scheme 4. Biaryl compounds **10-12** prepared from diazonium chlorides **1a-c** (ice cuboids) and 3-hydroxypyridine (**8**). ^aYield determined after column chromatography. ^bYield reported in literature for the addition of **1a-c** by syringe pump.¹⁴

3. Conclusion

In summary, these results demonstrate that the frozen diazonium chlorides are applicable in radical alkene and arene

functionalizations. The actual time of addition, resulting from the melting process of the ice sphere or cuboid, can be tuned through its dilution and through the method of addition from a few seconds to several minutes. In the case that the particular reaction is temperature sensitive, and the cooling impact through direct addition turns out to be unfavorable, slow melting in a funnel placed above the reaction vessel can be a useful alternative. Besides the advantage that frozen diazonium chlorides are storable without significant decomposition at -84°C for at least three weeks, the slow release of the diazonium ions by melting of the ice sphere or cuboid can replace the typically used syringe pump.

4. Experimental section

4.1. General techniques

Solvents and reagents were obtained from commercial sources and used as received. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded on *Bruker Avance 600* (^1H : 600 MHz; ^{13}C : 151 MHz) and *Bruker Avance 400* (^1H : 400 MHz; ^{13}C : 101 MHz) spectrometers. For $^1\text{H-NMR}$ spectra CDCl_3 , and CD_3OD were used as solvents. CHCl_3 (7.26 ppm), CD_3OH (3.31 ppm). Chemical shifts were reported in parts per million (ppm). Coupling constants were reported in Hertz (Hz). The following abbreviations were used for the description of signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet). $^{13}\text{C-NMR}$ spectra were recorded in CDCl_3 , and CD_3OD using CDCl_3 (77.16 ppm), and CD_3OD (49.05 ppm) as standard. Chemical shifts were given in parts per million (ppm). Analytical TLC was carried out on Merck silica gel plates using short wave (254 nm) UV light to visualize components. Silica gel (Kieselgel 60, 40-63mm, Merck) was used for flash column chromatography. For preparation of the respective ice cubes and ice spheres, two commercially available silicone trays (*Lurch*) were used.

4.2. Compounds

4.2.1. 4-Chlorophenyldiazonium chloride (**1**), 4-methoxyphenyldiazonium chloride (**1a**), 4-methylphenyldiazonium chloride (**1b**), 4-(methoxycarbonyl)phenyldiazonium chloride (**1c**)

To an ice-cooled degassed solution of the respective aniline (10.0 mmol) in HCl (3 N, 10 mL) and water (10 mL), a degassed solution of sodium nitrite (0.69 g, 10.0 mmol) in water (5 mL) was added dropwise by syringe pump over a period of 10 minutes. After stirring for an additional 20 minutes at 0°C , the 0.4 M solution of the diazonium chloride (**1**, **1a-c**) (10 mmol/25 mL) was used for preparation of various ice spheres (S) and ice cubes (C), or was directly added to the reaction mixtures in the case of reference experiments.

4.2.1.1. Preparation of ice cuboids (C) and ice spheres (S) for carboamination and carbohydroxylation:

Aliquots of the 4-chlorophenyldiazonium chloride (**1**) (2.5 mL, 0.40 M, 1 mmol, see above) were filled into the cavities of the silicone tray (cuboid shape or spherical shape, both from *Lurch*) using a syringe. The silicone tray was then placed into the fridge and stored at -84°C for at least three hours. Right before the respective reaction, the silicone tray was taken from the fridge and the ice cuboid or sphere was easily detached from the tray using a tweezer.

4.2.1.2. Preparation of diluted ice cuboids (C) for biaryl synthesis:

Aliquots of the diazonium chloride (**1** and **1a-c**) (2.5 mL, 0.40 M, 1 mmol, see above) were filled into the cavities of the silicone tray (cuboid shape, *Lurch*) using a syringe. Afterwards, water (4.5 mL) was added to each previously filled cavity. Then, the silicone tray was placed into the fridge and stored at -84°C for one day. Right before the respective reaction, the silicone tray was taken from the fridge and the ice cuboid was easily detached from the tray using a tweezer.

4.2.2. (*E*)-4-(4-Chlorophenyl)-((4-chlorophenyl)-diazenyl)-3-methylbutan-1-ol (**3**).

4.2.2.1. Synthesis using a syringe pump (reference experiment)

To a stirred solution of the 3-methyl-3-buten-1-ol (**2**) (1.21 mL, 12.0 mmol) and Na_2CO_3 (477 mg, 4.50 mmol) in acetonitrile/water (1:1, 5 mL) at 50°C , an aliquot of the 0.4 M 4-chlorophenyldiazonium chloride solution (**1**) (2.5 mL, 1.00 mmol) was added dropwise over 5 minutes via syringe pump. After stirring for 10 minutes at 50°C , the reaction mixture was diluted with water (10 mL) and extracted with MTBE (3×30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4 . The solvents were removed under reduced pressure. The yield of **3** (81.0 mg, 0.24 mmol, 48%) was determined by $^1\text{H-NMR}$ using dimethyl terephthalate as internal standard.

4.2.2.2. Synthesis via direct addition of ice sphere

To a vigorously stirred solution of the 3-methyl-3-buten-1-ol (**2**) (1.21 mL, 12.0 mmol) and Na_2CO_3 (477 mg, 4.50 mmol) in acetonitrile/water (1:1, 5 mL) in a 50 mL wide-neck (NS 29/32) round-bottom flask at 50°C was added a frozen ice sphere (-84°C , 3.0 h freezing time) of 4-chlorophenyldiazonium chloride (**1**) (2.5 mL, 0.4 M, 1.00 mmol) (see preparation 4.2.1.1). After the melting process (ca. 25 s), the reaction mixture was stirred for a further 15 minutes at 50°C . Afterwards, the reaction mixture was diluted with water (10 mL) and extracted with MTBE (3×30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4 . The solvents were removed under reduced pressure. The yield was determined by $^1\text{H-NMR}$ using dimethyl terephthalate as internal standard (55%). Then the product was purified by column chromatography on silica gel (hexane/EtOAc = 4:1) and gave **3** (97.9 mg, 0.29 mmol, 57%) as orange oil.

4.2.2.3. Synthesis through addition of ice sphere via funnel

Onto a vigorously stirred solution of the 3-methyl-3-buten-1-ol (**2**) (12.0 mmol, 1.21 mL) and Na_2CO_3 (477 mg, 4.50 mmol) in acetonitrile/water (1:1, 5 mL) in a 25 mL narrow-neck round-bottom flask at 50°C was placed a glass funnel with a drop opening of around 6 mm. Then, a frozen ice sphere (-84°C , 3.0 h freezing time) of 4-chlorophenyldiazonium chloride (**1**) (2.5 mL, 0.4 M, 1.00 mmol) (see preparation 4.2.1.1) was placed into the funnel. When melting of the sphere and thus the addition was completed after ca. 10 minutes, the reaction mixture was stirred for another 15. The reaction mixture was diluted with water (10 mL) and extracted with MTBE (3×30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4 . The solvents were removed under reduced pressure. The yield of **3** (42%) was determined by $^1\text{H-NMR}$ of the crude product with internal standard.

$R_f = 0.2$ (hexane/EtOAc = 4:1) [UV]. $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ (ppm) = 1.23 (s, 3 H), 1.96 (bs, 1 H), 1.96 (td, $J = 6.3$

Hz, $J = 14.1$ Hz, 1 H), 2.19 (td, $J = 6.2$ Hz, $J = 14.1$ Hz, 1 H), 3.04 (d, $J = 13.2$ Hz, 1 H), 3.14 (d, $J = 13.1$ Hz, 1 H), 3.77 (td, $J = 6.3$ Hz, $J = 11.0$ Hz, 1 H), 3.85 (td, $J = 6.2$ Hz, $J = 11.0$ Hz, 1 H), 6.99 (d, $J = 8.4$ Hz, 2 H), 7.18 (d, $J = 8.4$ Hz, 2 H), 7.44 (d, $J = 8.7$ Hz, 2 H), 7.59 (d, $J = 8.7$ Hz, 2 H). $^{13}\text{C-NMR}$ (300 MHz, CDCl_3): δ (ppm) = 21.9, 41.3, 44.8, 59.1, 73.4, 123.4, 128.0, 129.3, 132.0, 132.3, 135.6, 136.7, 149.9. The analytical data obtained is in agreement with the data reported in literature.¹¹

4.2.3. 1-(4-Chlorophenyl)-2-phenylpropan-2-ol (**5**)

4.2.3.1. Synthesis using a syringe pump (reference experiment)

To a stirred solution of α -methylstyrene (**4**) (0.78 mL, 6.00 mmol) and KOAc (442 mg, 4.50 mmol) in acetonitrile/water (5:1, 6 mL) at 70 °C, a solution of 4-chlorophenyldiazonium chloride (**1**) (2.5 mL, 0.4 M, 1.00 mmol) was added dropwise over 5 minutes via syringe pump. After stirring for 10 minutes at 70 °C, the reaction mixture was diluted with water (10 mL), cooled to room temperature and extracted with MTBE (3 \times 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4 . The solvents were removed under reduced pressure. The yield of **5** (155 mg, 0.63 mmol, 63%) was determined by $^1\text{H-NMR}$ using dimethyl terephthalate as internal standard.

4.2.3.2. Synthesis through addition of ice sphere via funnel

Onto a stirred solution of α -methylstyrene (**4**) (0.78 mL, 6.00 mmol) and KOAc (442 mg, 4.50 mmol) in acetonitrile/water (5:1, 6 mL) in a 25 mL narrow-neck round-bottom flask at 70 °C was placed a glass funnel with a drop opening of around 6 mm. Then, a frozen ice sphere (-84 °C, 3.0 h freezing time) of 4-chlorophenyldiazonium chloride (**1**) (0.4 M, 2.5 mL, 1.0 mmol) (see preparation 4.2.1.1) was placed into the funnel. After melting of the sphere was completed (ca. 10 minutes), the reaction mixture was stirred for another 15 minutes at 70 °C. The reaction mixture was diluted with water (10 mL) and extracted with MTBE (3 \times 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4 . The solvents were removed under reduced pressure. The yield was determined by $^1\text{H-NMR}$ using dimethyl terephthalate as internal standard (59%). Then the product was purified by column chromatography on silica gel (hexane/EtOAc = 6:1) and gave pure **5** (153 mg, 0.62 mmol, 62%) as yellow oil.

$R_f = 0.5$ (hexane/EtOAc = 4:1) [UV]. $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ (ppm) = 1.56 (s, 3 H), 1.78 (bs, 1 H), 2.99 (d, $J = 13.1$ Hz, 1 H), 3.06 (d, $J = 13.2$ Hz, 1 H), 6.88 (d, $J = 8.4$ Hz, 2 H), 7.15 (d, $J = 8.4$ Hz, 2 H), 7.22-7.25 (m, 1 H), 7.29-7.33 (m, 2 H), 7.33-7.36 (m, 2 H). $^{13}\text{C-NMR}$ (300 MHz, CDCl_3): δ (ppm) = 29.3, 49.8, 74.5, 124.9, 126.8, 128.1, 128.1, 131.8, 132.5, 135.3, 147.1. The analytical data obtained is in agreement with the data reported in literature.¹²

4.2.4. (5-(4-Chlorophenyl)furan-2-yl)methanamine (**7**)

The diluted 4-chlorophenyldiazonium chloride (**1**) ice cuboid (**C**) (7.0 mL, 1.0 mmol) (see preparation 4.2.1.2) was added to a vigorously stirring solution of furfurylamine (**6**) (925 μL , 10 mmol) in 2 mL 6 N HCl and TiCl_3 (ca. 1 M solution in 3 N HCl, 2 mL, 2 mmol) under nitrogen atmosphere at room temperature. After melting of the ice cuboid (ca. 7 minutes), the resulting mixture was stirred for a further 25 minutes. Then, water (100 mL) was added and the pH-value was adjusted to pH

>12 using an aqueous 2 N NaOH solution. After extraction with ethyl acetate (3 \times 150 mL), the combined organic phases were washed with saturated aqueous sodium chloride (100 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the desired crude product **7**. The yield of **7** (54%) was determined by $^1\text{H-NMR}$ using dimethyl terephthalate as internal standard. Purification by chromatography ($\text{CHCl}_3/\text{MeOH} = 20:1$) gave a pure sample of **7**.

$R_f = 0.4$ ($\text{CHCl}_3/\text{MeOH} = 5:1$) [UV]. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.66 (bs, 2H), 3.89 (bs, 2H), 6.23 (d, $J = 3.3$ Hz, 1H), 6.56 (d, $J = 3.3$ Hz, 1H), 7.34 (d, $J = 8.7$ Hz, 2H), 7.58 (d, $J = 8.7$ Hz, 2H). $^{13}\text{C-NMR}$ (151 MHz, CDCl_3) δ 39.5, 106.1, 107.4, 124.8, 128.8, 129.4, 132.7, 152.0, 156.7. The analytical data obtained is in agreement with the data reported in literature.¹³

4.2.5. 2-(4-Chlorophenyl)pyridin-3-ol (**9**)

The diluted 4-chlorophenyldiazonium chloride (**1**) ice cuboid (**C**) (7.0 mL, 1.0 mmol) (see preparation 4.2.1.2) was added to a vigorously stirring solution of 3-hydroxypyridine (**8**) (951 mg, 10 mmol) in 2 mL 6 N HCl and TiCl_3 (ca. 1 M solution in 3 N HCl, 1 mL, 1 mmol) under nitrogen atmosphere at room temperature. After melting of the ice cuboid (ca. 7 minutes), the resulting mixture was stirred for a further 25 minutes. Then, water (100 mL) was added and the pH-value was adjusted to pH 9-10 using saturated sodium carbonate solution. After extraction with ethyl acetate (3 \times 150 mL), the combined organic phases were washed with saturated aqueous sodium chloride (100 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the desired crude product. Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **9** (142 mg, 0.69 mmol, 69%) as a white solid.

$R_f = 0.4$ (5:1 chloroform/diethyl ether). $^1\text{H-NMR}$ (400 MHz, CD_3OD) 7.23 (dd, $J = 8.2, 4.6$ Hz, 1H), 7.33 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.43 (d, $J = 8.8$ Hz, 2H), 7.87 (d, $J = 8.8$ Hz, 2H), δ 8.10 (dd, $J = 4.6, 1.4$ Hz, 1H). $^{13}\text{C-NMR}$ (151 MHz, CD_3OD) δ 125.1, 125.3, 129.1, 131.9, 135.1, 137.5, 141.2, 146.0, 153.4. The analytical data obtained is in agreement with the data reported in literature.¹⁴

4.2.6. 2-(4-Methoxyphenyl)pyridin-3-ol (**10**)

Biaryl **10** was prepared from diazonium salt **1a** analogously to the procedure described for biaryl **9**. The product was purified by column chromatography on silica gel ($\text{CHCl}_3/\text{MTBE} = 6:1$ to 1:1) and gave pure **10** (120 mg, 0.60 mmol, 60%) as light brown solid.

$R_f = 0.3$ ($\text{CHCl}_3/\text{MTBE} = 5:1$) [UV]. $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ 3.80 (s, 3H), 6.94-7.00 (m, 2H), 7.14 (dd, $J = 8.2, 4.7$ Hz, 1H), 7.28 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.80-7.83 (m, 2H), 8.04 (dd, $J = 4.7, 1.4$ Hz, 1H). $^{13}\text{C-NMR}$ (101 MHz, CD_3OD) δ 55.7, 114.3, 124.1, 125.0, 131.0, 131.6, 140.6, 147.2, 153.0, 161.2. The analytical data obtained is in agreement with the data reported in literature.¹⁴

4.2.7. 2-(*p*-Tolyl)pyridin-3-ol (**11**)

Biaryl **11** was prepared from diazonium salt **1b** analogously to the procedure described for biaryl **9**. The product was purified by column chromatography on silica gel ($\text{CHCl}_3/\text{MTBE} = 8:1$ to 1:1) and gave pure **11** (97 mg, 0.52 mmol, 52%) as light brown solid.

$R_f = 0.3$ (CHCl₃/MTBE = 5:1) [UV]. ¹H-NMR (400 MHz, CD₃OD) δ 2.38 (s, 3H), 7.18 (dd, $J = 8.2, 4.7$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.30 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 8.06 (dd, $J = 4.7, 1.3$ Hz, 1H). ¹³C-NMR (101 MHz, CD₃OD) δ 21.3, 124.4, 125.1, 129.6, 130.2, 135.8, 139.2, 140.7, 147.5, 153.2. The analytical data obtained is in agreement with the data reported in literature.¹⁴

4.2.8. Methyl 4-(3-hydroxypyridin-2-yl)benzoate (**12**)

Biaryl **12** was prepared from diazonium salt **1c** analogously to the procedure described for biaryl **9**. The product was purified by column chromatography on silica gel (CHCl₃/MTBE = 7:1 to 1:1) and gave pure **12** (90 mg, 0.39 mmol, 39%) as light yellowish-brown solid.

$R_f = 0.3$ (CHCl₃/MTBE = 5:1) [UV]. ¹H-NMR (400 MHz, CD₃OD) δ 3.93 (s, 3H), 7.27 (dd, $J = 8.3, 4.6$ Hz, 1H), 7.36 (dd, $J = 8.3, 1.4$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 2H), 8.08 (d, $J = 8.8$ Hz, 2H), 8.14 (dd, $J = 4.6, 1.4$ Hz, 1H). ¹³C-NMR (101 MHz, CD₃OD) δ 52.7, 125.4, 125.5, 130.1, 130.4, 130.6, 141.4, 143.6, 145.8, 153.6, 168.4. The analytical data obtained is in agreement with the data reported in literature.¹⁴

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Supplementary Material

Supplementary data (¹H NMR and ¹³C NMR spectra of compounds **3**, **5**, **7** and **9-12**; optimization for radical arylation of **6** and **8**) associated with this article can be found in the online version.....