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Synthesis of a (piperazin-1-ylmethyl)biaryl library via microwave-mediated Suzuki–Miyaura cross-couplings

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ABSTRACT

Boc-protected (piperazin-1-ylmethyl)biaryls have been synthesised from (Boc-piperazin-1-ylmethyl) phenylboronic acid pinacol esters via a microwave-mediated Suzuki–Miyaura coupling with aryl bromides viz. 1-bromo-, 2-, 3- or 4-nitrobenzene or 2-bromo-5-nitropyridine. Judicial removal of the protecting group on the piperazine, or facile reduction of the nitro group on the biaryl system enabled the manipulation of two points of functionality in order to diversify the scope of the resulting biaryl library.

The biaryl unit is found in many natural and synthetic products and as a privileged scaffold in medicinal chemistry. Undoubtedly, the most important and efficient strategy for its construction is the palladium-catalyzed Suzuki–Miyaura (SM) coupling reaction.[1]

The incorporation of a piperazine motif into a molecule is interesting from a medicinal chemistry point of view since it produces analogues that have a lower lipophilicity and enhances aqueous solubility.[2] Hence, piperazine units are found in many drugs with a broad scope of actions such as antidepressants,[3] antihistamines,[4] antiretrovirals,[5] anti-Parkinson's,[6] antianginals[7] and antipsychotics[8] amongst others (Fig. 1).[9–11]

Recently, we reported the synthesis of an arylboronate library using microwave-mediated S_N2 reactions of (bromomethyl)phenylboronic acid pinacol esters with a range of *N*-, *S*- and *O*-nucleophiles.[12] These were further reacted to afford a library of biaryls. In certain instances, Boc-piperazine was used as an *N*-nucleophile and the arylboronic esters obtained were found to be interesting because the protecting group on the piperazine could be easily removed to liberate an amine, allowing further functionalisation prior to, or following, a Suzuki–Miyaura cross-coupling with various aryl halides.

Herein, we describe the use of protected *m*- or *p*-substituted (piperazin-1-ylmethyl)phenylboronic acid pinacol esters **1** as useful synthons for the synthesis of a wide range of biaryls. As a starting point, we have repeated or elaborated upon our previous findings, in order to increase the scope of the SM coupling reaction

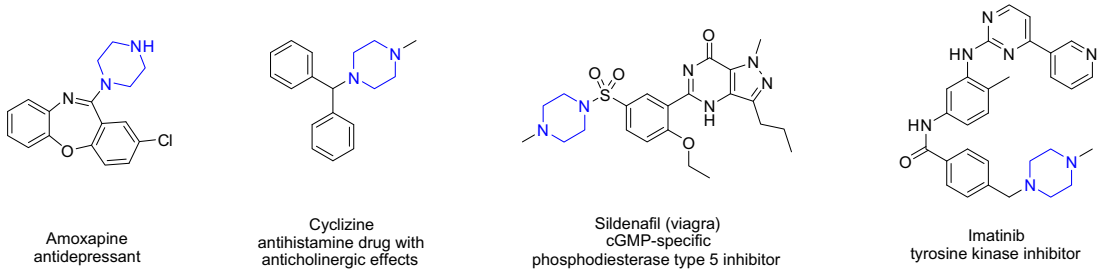

Figure 1. Examples of drugs containing the piperazine motif (in blue).

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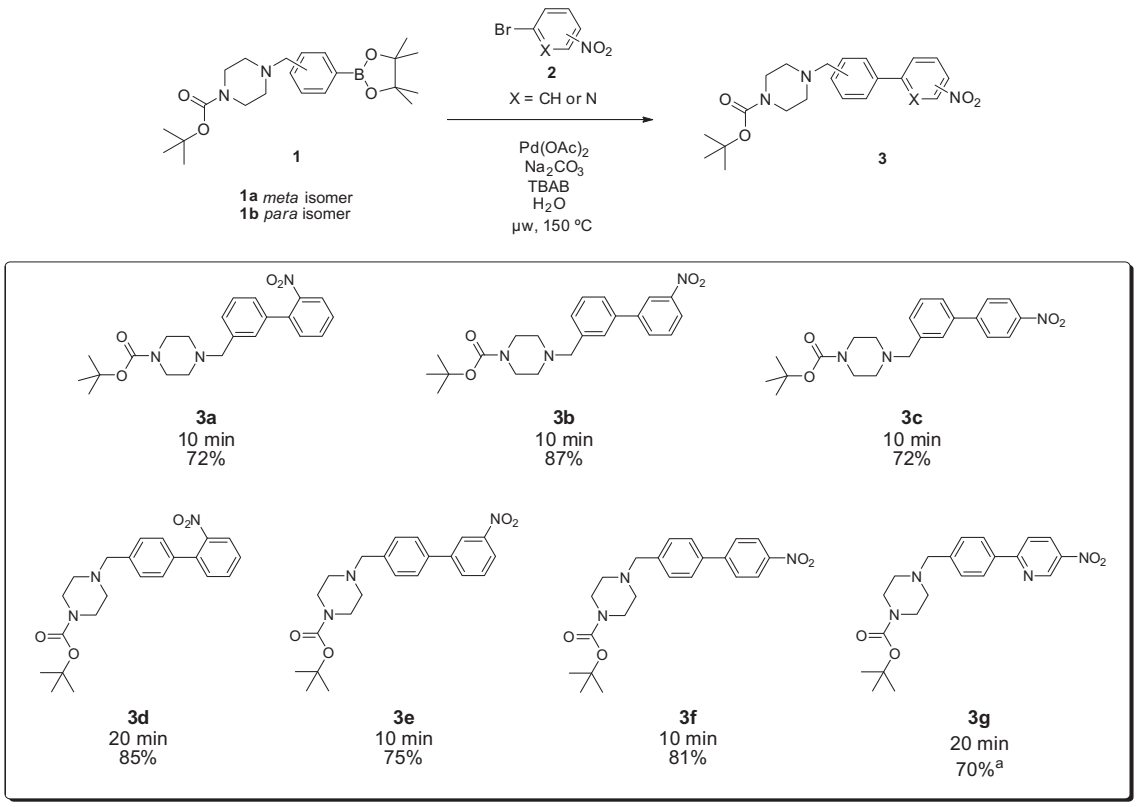
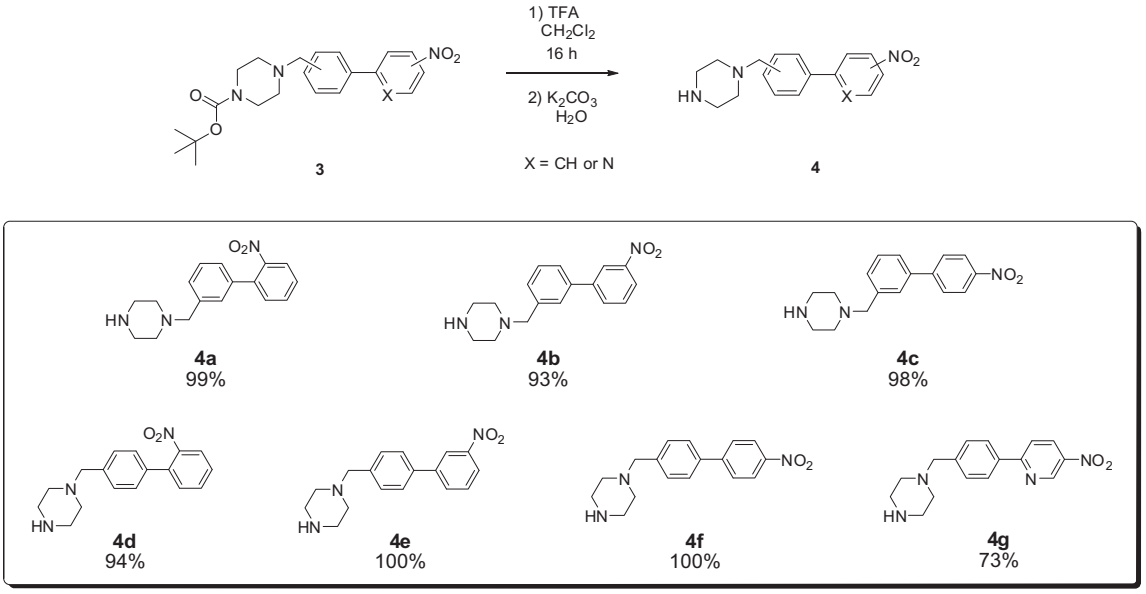


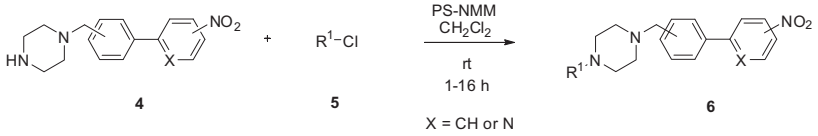
Scheme 1. SM reactions on compounds **1**. Reaction yields given after purification by chromatography. Reaction times given in minutes (min). [a]$Pd(PPh_3)_4$ used as precatalyst (3 mol %), Na_2CO_3 (3 equiv) in toluene/EtOH/H_2O (1:1:1), 150 °C, microwave irradiation (maximum power 300 W).

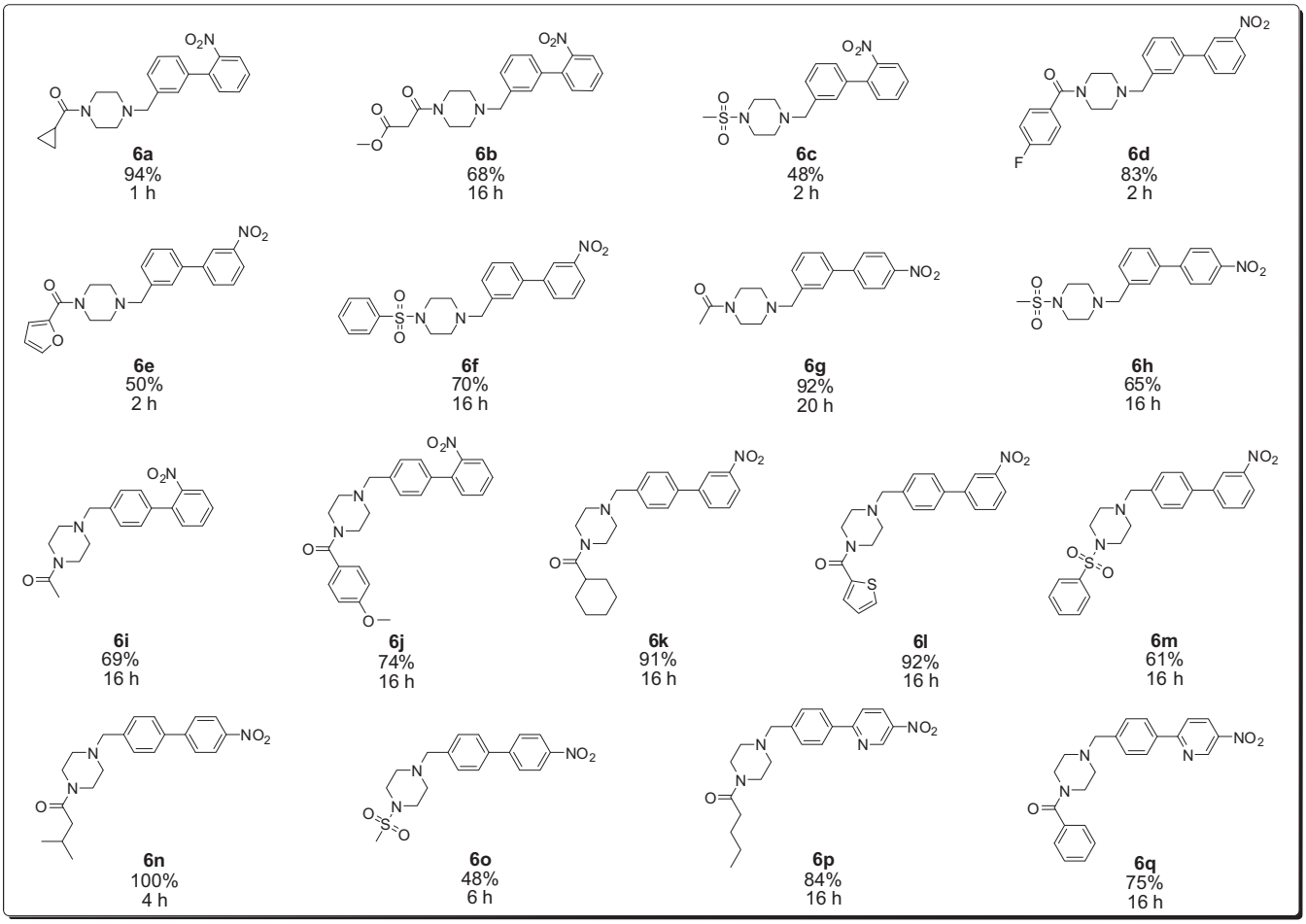


Scheme 2. Cleavage of the Boc group in **3**. Crude reaction yields given as the products were used without further purification.

of **1**. The isomeric 2-methylphenylboronic acid pinacol esters were previously shown to deprotodeborylate in SM reactions and so were not selected.[13] We also found that *N*-substituted 3- and 4-methylphenylboronic acid pinacol esters could react with different aryl bromides in a Suzuki–Miyaura cross-coupling using microwave-assisted organic synthesis (MAOS) to afford the corresponding biphenyl compounds. 2-, 3- and 4-bromo-nitrobenzenes and 2-bromo-5-nitropyridine **2** were used as aryl halides partly due to their facile coupling in the SM process, but also because the nitro groups can be reduced at a later stage to anilines, which can be functionalised leading to diversity in the final library.

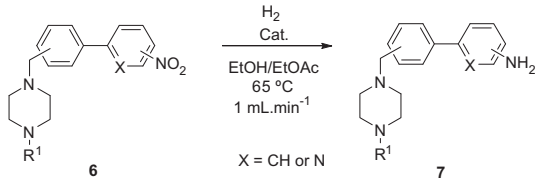
The SM coupling was achieved employing Leadbeater's conditions[14] with palladium(II) acetate as the precatalyst and **2** as aryl bromides under microwave irradiation (μw) on compounds **1a** and **1b**. The expected biphenyls were obtained in good yields, within 10–20 min (Scheme 1).

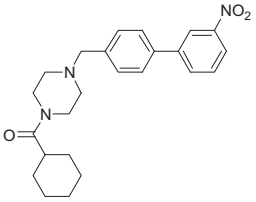
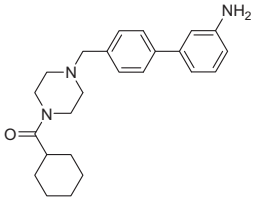




Scheme 3. Functionalisation of compounds **4** to afford **6**. Reaction yields given after purification by chromatography. Reaction times given in hours (h).

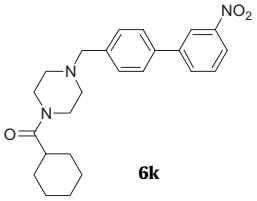
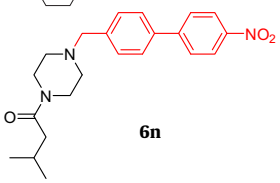
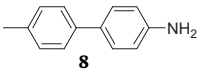
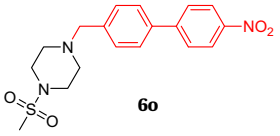
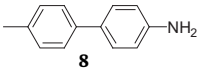
Table 1
Optimisation of the nitro group reduction of **6**



Entry	**6**	Conditions	Product	Yield (%)
1	 **6k**	Raney Ni/H_2	 **7a**	94

(*continued on next page*)

Table 1 (*continued*)

Entry	6	Conditions	Product	Yield (%)
2	 **6k**	$SnCl_2 \cdot 2H_2O$	**7a**	67[a]
3	 **6n**	$Pd/C/H_2$	 **8**	97
4	 **6o**	$Pd/C/H_2$	 **8**	94

[a] Microwave irradiation (maximum power 300 W), EtOH, 130 °C, 30 min.

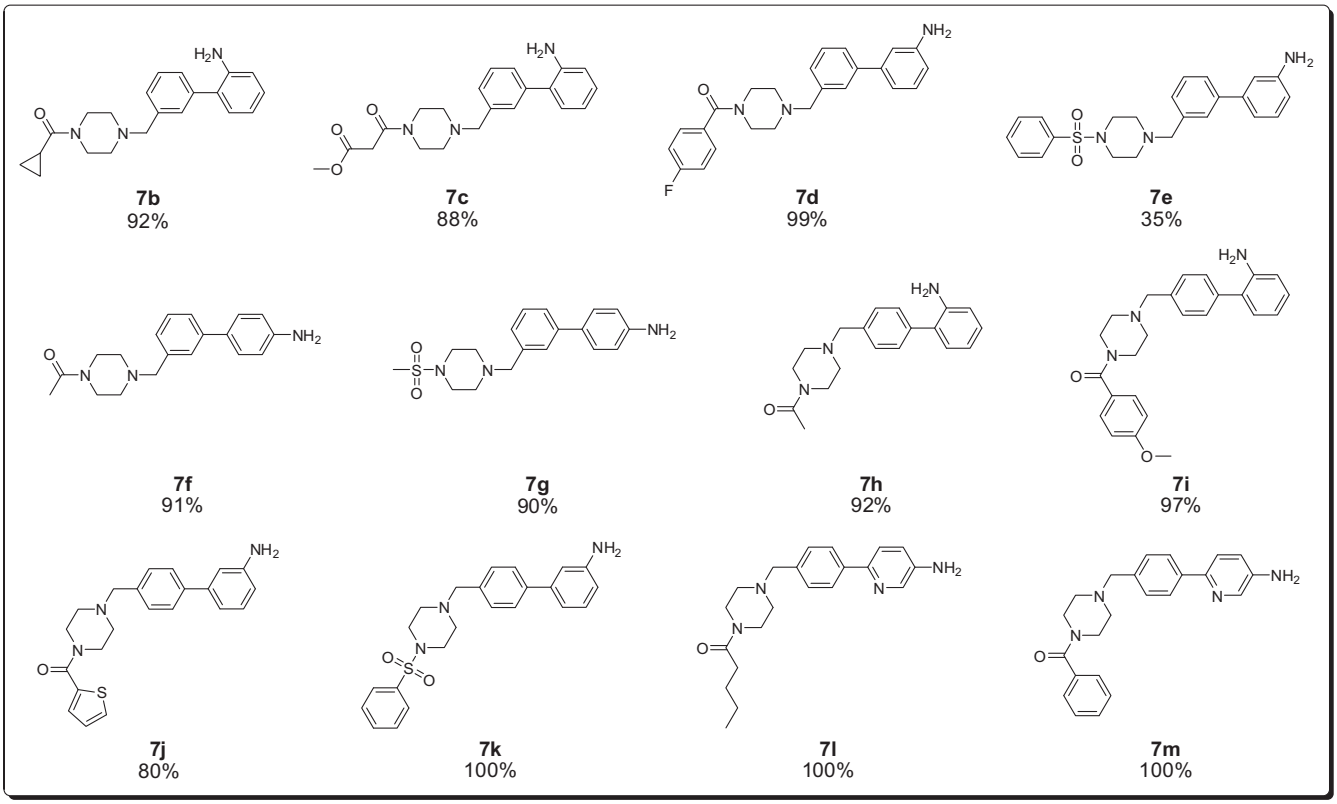
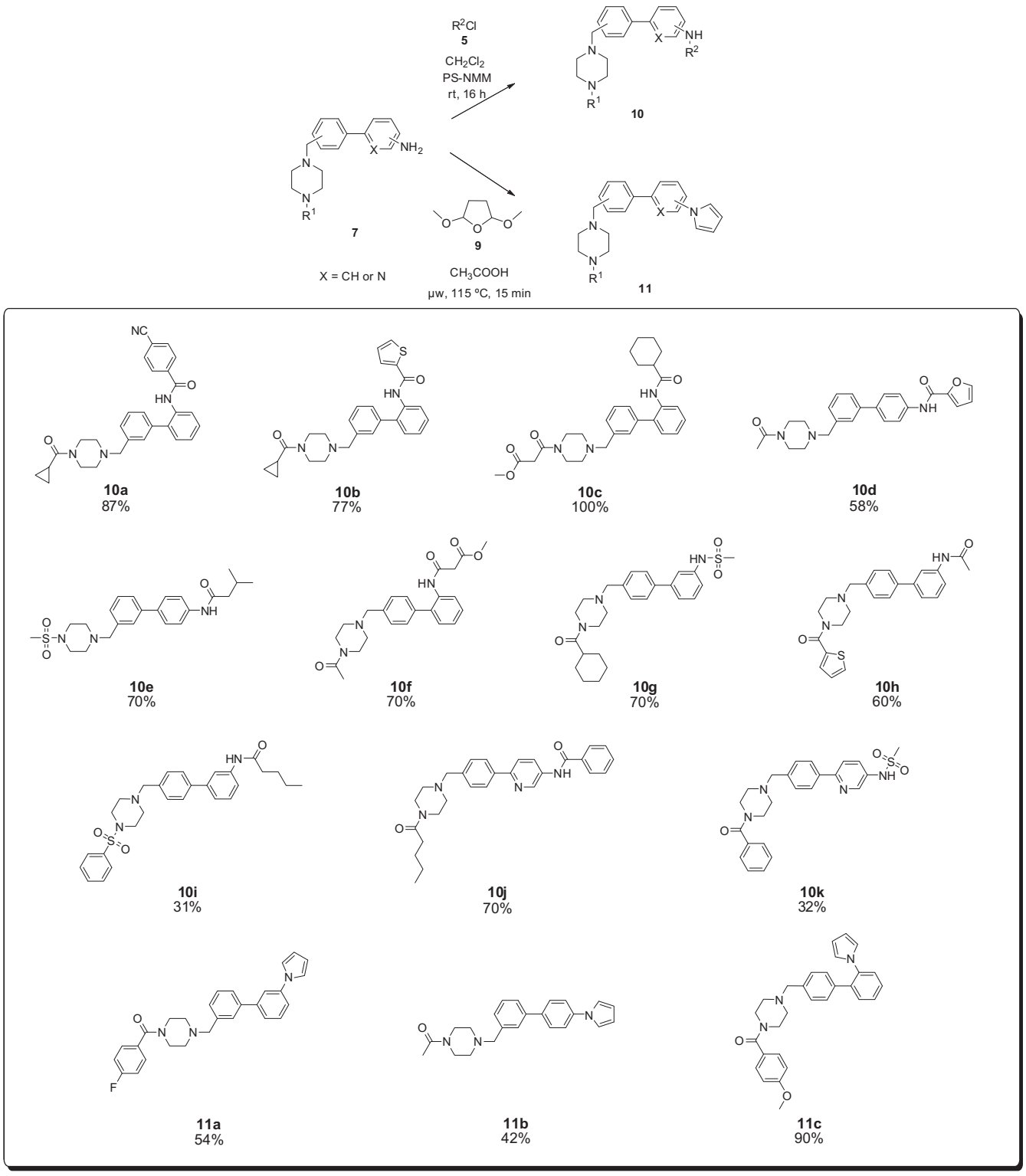


Figure 2. Amines **7** synthesised using Raney Nickel/H-Cube conditions. Crude reaction yield given as the products were used without further purification.

Once the biphenyl unit had been synthesised, the functionalisation reactions could be initiated. Boc group cleavage was achieved with trifluoroacetic acid (TFA) in dichloromethane at room temperature within 2 h or overnight, followed by a basic work-up to liberate the free amine (Scheme 2).[15]

Compounds **4** were functionalised by reaction with acid or sulfonyl chlorides **5** in dichloromethane at room temperature in the presence of a supported base (PS-NMM: polystyrene *N*-methylmorpholine) (Scheme 3).[16] The amidation reaction gave the expected products in good yields (e.g., **6a** in 94% yield) while the sulfonylation process afforded the corresponding products in moderate yields (e.g., **6c** in 48% yield). Most reactions with acid chlorides worked very well in a few hours (e.g., **6a** in 94% yield in 1 h, **6d** in 83% yield in 2 h and **6n** in 100% yield in 4 h), whereas some required an overnight reaction to give the expected products in moderate yields (e.g., **6i** in 69% yield and **6m** in 61% yield).

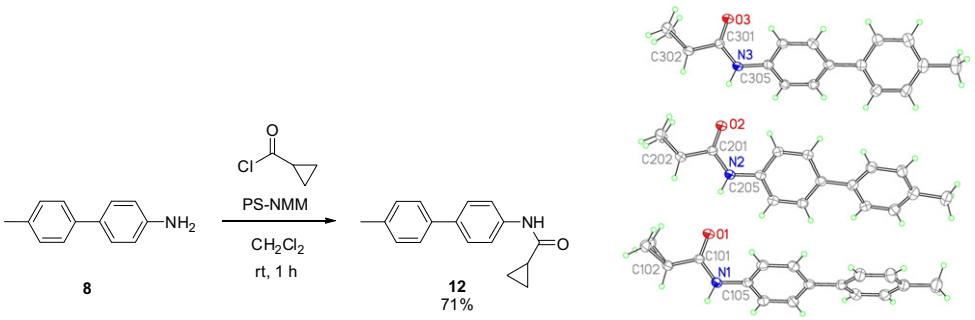
We next intended to reduce the nitro group in compounds **6** in order to produce amines for further functionalisation reactions. Nitro group reduction can be performed by thermal, microwave or flow chemistry (H-Cube)[17] routes. We found the latter to be



Scheme 4. Amine functionalisation reactions of compounds **7**. Reaction yields given after purification by chromatography.

the most straightforward option since it generally obviated a purification or work-up step. The attempted reduction of nitro-biphenyl derivatives was mainly investigated in an H-Cube, in ethanol/ethyl acetate (1:1), at 65 °C, with a flow rate of 1 mL min^{-1} and in full hydrogen mode, as outlined in Table 1.

When Raney Nickel was used as the catalyst, the expected product **7a** was obtained in very good yield (Table 1, entry 1). A microwave-mediated nitro reduction was attempted using tin chloride dihydrate (entry 2), but gave an inferior yield and a more complicated work-up, compared with the former reduction. However, unexpected hydrogenolysis of the benzylic-like unit in **6n** and **6o** led to the corresponding 4-tolylaniline **8** when Pd/C and H_2 were used (Table 1, entries 3 and 4). This is akin to a standard debenzylation reaction in organic synthesis.[15] Thereafter, the Raney Nickel/



Scheme 5. Amine functionalisation reaction of compound **8** and the asymmetric unit of the crystal structure of **12**. Reaction yield given after purification by chromatography.

H-cube conditions were used to reduce the other (piperazin-1-ylmethyl)nitrobiphenyl derivatives (Fig. 2). Many of the products **7** were obtained in very good yields without any further purification.

The amine group could next be functionalised by amidation and sulfonylation reactions with the corresponding acid or sulfonyl chlorides **5** in the presence of a supported base (PS-NMM). Pyrrole derivatives were synthesised by reaction of **7** with 2,5-dimethoxytetrahydrofuran (**9**) in acetic acid (Scheme 4)[18]

The elaborated biaryl products were obtained in moderate to good yields after purification by chromatography on silica gel. An amide coupling of **8** led to an interesting biphenyl derivative **12** in good yield (Scheme 5). Very small crystals of **12** were grown and analysed by a synchrotron X-ray diffraction crystal structure determination which shows a very interesting structure with a Z' value of 3 (Supplementary data, S19).

In summary, a (piperazin-1-ylmethyl)biaryl library has been synthesised over a few steps using, inter alia, the MAOS-mediated Suzuki-Miyaura coupling reaction. This library is composed of a number of very interesting drug-like molecules. The crystal structure of **12** has stimulated our interest into examining analogues in the solid state and results will be disclosed in due course.

Acknowledgements

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Supplementary data

Supplementary data (general procedures, analytical data for compounds and crystallography data (CCDC 810173)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.025.

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