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Palladium catalysed sequential imine arylation/Suzuki–Miyaura coupling: synthesis of α-(biarylyl)benzylamines

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ABSTRACT

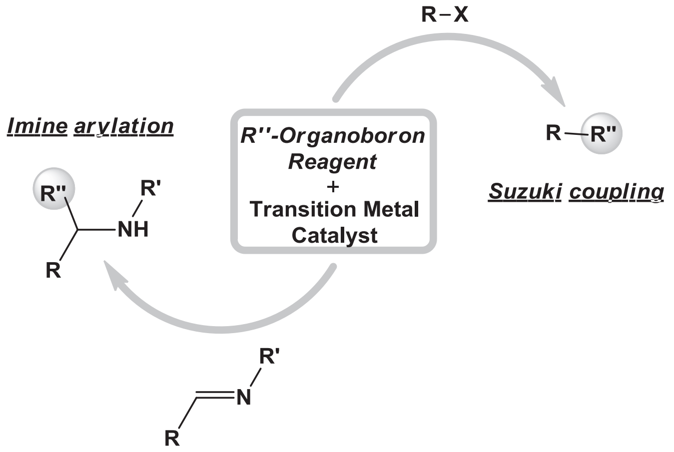
We report an innovative, high yielding one-pot sequential catalytic imine arylation/Suzuki–Miyaura cross-coupling reaction, which converts suitably activated imine substrates to various biarylarylmethyl amine products using several commercial Pd catalysts. Many biarylarylmethyl amine molecules are biologically active. Insightful computational studies detail the mechanism of the imine arylation process. The sequence of reactions is likely to be dependent on the reaction conditions.

1. Introduction

The formation of carbon–carbon single bonds, which lies at the heart of organic chemistry, is today still an enormous challenge for synthetic chemists in many contexts. Over the last number of years great efforts have been made by synthetic chemists to develop concise sequential or cascade catalytic processes for the construction of multiple bonds and the formation of complex structures.[1] Such processes are attractive for reasons of: cost, time, energy consumption and waste reduction. Transition metal catalysts are generally involved.[2] Success with such processes relies on the types of catalysis involved and their compatibility. Two powerful synthetic methodologies that are available to chemists are the Suzuki–Miyaura cross-coupling reaction and the catalytic arylation of imines, both relying on arylboronic acids and derivatives (Scheme 1).[3,4]

Our group is active in this field, having used transition metal catalysts and arylboron reagents for the synthesis of chiral amine units.[4a,5] This methodology has been extended recently, to the formation of α-hydroxyesters[6] and α-amino acid derivatives.[7]

The synthesis of biarylarylmethyl amine (α-(biphenylyl)benzylamine) units is important, considering their presence in some biologically active compounds. Bifonazole (α-(4-biphenylyl)benzyl imidazole, Fig. 1) is a strong antifungal agent, which has been used in the treatment of skin infections.[8a,b] Another example is the potent γ-secretase modulator BIIB042 (Fig. 1), which, contains a 2-phenylbenzylamine.[8c,d] (In fact, we have an active programme running looking at new drugs for treating Alzheimer's disease and this target is of significance to us). Other similar compounds having biological interest, and whose structures are close to the target unit are Valsartan[8e] (Diovan®)—an important angiotensin receptor blocker indicated for treatment of high blood pressure, congestive



Scheme 1. Formation of carbon–carbon single bonds using the Suzuki–Miyaura cross-coupling and the arylation of imines.

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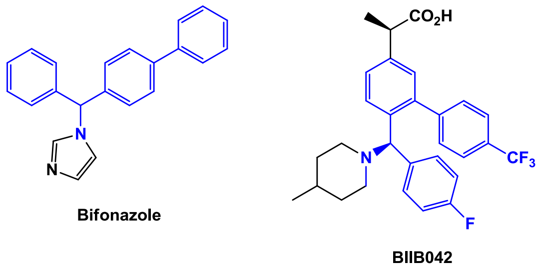
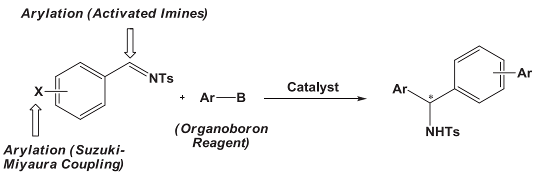


Fig. 1. Some pharmacologically active compounds containing a biarylarylmethylamine unit.

heart failure or post-myocardial infarction, but also the well-known glycopeptide antibiotic, Vancomycin[8f] used for prophylaxis and treatment of infections caused by Gram-positive bacteria. These units—particularly chiral ones—are also of interest for the construction of certain electronic materials, e.g. liquid crystals.[9]

Biaryl scaffolds can currently be accessed by a variety of cross-coupling methods, which includes one-pot processes.[10] Some important developments have come from the laboratories of Lautens who reported an elegant tandem Pd-catalysed Suzuki–Miyaura/direct arylation reaction,[11a] Gembus et al. who reported a Pd-catalysed one-pot sequential Suzuki–Miyaura/direct C–H functionalization of imidazo[1,2-a]pyrazines,[11b] and Bedford's group who reported a novel catalytic one-pot synthesis of carbazoles via consecutive amination and C–H activation.[11c] Although C–H activation methods[10c] are the most effective current approach, as a starting point, we decided to investigate the feasibility of a tandem or sequential catalytic one-pot reaction for the creation of interesting biarylarylmethylamine units (Scheme 2).



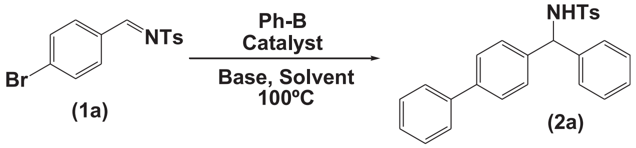
Scheme 2. Sequential one-pot C–C bond-forming catalytic reactions.

2. Results and discussion

Using the aldimine (**1a**) as substrate, we carried out a screening study of a variety of viable palladium catalysts, including, solvents and additives. Our preliminary results, targeting 4-arylbenzylamines, are shown in Table 1. Starting with $Pd(OAc)_2$ and PPh_3 in the presence of phenylboronic acid in toluene, the reaction ran smoothly giving the α-biarylyl benzyl amine (**2a**) in 38% yield (2 steps) (Table 1, entry 1). The use of NaOMe instead of NEt_3 increased the yield to 58% (Table 1, entry 3). When Ph_3B was used as the organoboron source (Table 1, entry 4) a yield of 58% was obtained. The commercial PEPPSI-IPr catalyst (Fig. 2), already used successfully in the Negishi cross-coupling reaction,[12] including interesting applications in the Kumada–Tamao–Corriu reaction,[13] was also investigated.

Upon screening a variety of solvents, it seemed that non-polar solvents like toluene or non-protic polar solvents like, THF (Table 1, entries 5 and 6, respectively) gave the best results. Phenylboronic acid (Table 1, entries 5–7) and sodium tetraphenylborate ($NaPh_4B$) (Table 1, entry 8) gave the expected product. Gratifyingly, $NaPh_4B$ gave the product (**2a**) in almost quantitative yield after only 18 h. (**2a**) was not obtained using other boron reagents, like $PhBF_3K$, $(PhBO)_3$, $C_9H_{11}BO_2$ and Ph_3B with PEPPSI-IPr and NEt_3 in toluene. In fact, in all the test reactions (Table 1) small quantities of the intermediate *p*-bromophenylphenylmethylamine (**3a**) (Scheme 3, (**3a**)) were detected by HPLC, thus suggesting a sequential catalytic event and not a tandem process.[1a] *para*-Bromophenyl alcohol (**4**) (Scheme 3) was also detected by TLC and HPLC analysis. (**4**) arises from hydrolysis of the aldimine to the aldehyde followed by subsequent arylation of the aldehyde.

Table 1
Optimization of the reaction conditions at 100 °C



Entry[a]	Ph-B	Catalyst	Base	Solvent	Tr/h	Yield[b]/%
1	$PhB(OH)_2$	$Pd(OAc)_2/PPh_3$	NEt_3	Toluene	16	38
2	$PhB(OH)_2$	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	Toluene	40	13
3	$PhB(OH)_2$	$Pd(OAc)_2/PPh_3$	NaOMe	Toluene	40	58
4	Ph_3B	$Pd(OAc)_2/PPh_3$	NEt_3	Toluene	21	58
5	$PhB(OH)_2$	PEPPSI-IPr	NEt_3	Toluene	19	36
6	$PhB(OH)_2$	PEPPSI-IPr	NEt_3	THF	18	49
7	$PhB(OH)_2$	PEPPSI-IPr	NEt_3	DME	18	15
8	$NaPh_4B$	PEPPSI-IPr	NEt_3	Toluene	18	95
9	$NaPh_4B$	PEPPSI-IPr	Cs_2CO_3	Toluene	18	9

[a] Reagents and conditions: catalyst (3 mol %), Ph-B (4 equiv), base (4 equiv), solvent (2 mL), 100 °C, rt.

[b] Overall isolated yield from two steps, after liquid chromatography on silica gel.

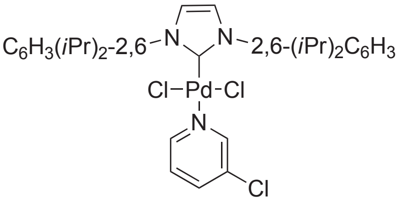


Fig. 2. PEPPSI-IPr catalyst.

A final test reaction was made using $NaPh_4B$ (and PEPPSI-IPr catalyst) instead of $PhB(OH)_2$ (Table 1, compare entry 2 with entry 9) but no improvements in the yield were observed. In order to test the scope of this method we applied our best conditions obtained so far (3 mol % PEPPSI-IPr along with $NaPh_4B$ (4 equiv) and NEt_3 (4 equiv) in toluene at 100 °C) to a series of activated aldimine substrates. To widen the scope further, we decided to extend our study to the biphenyl isomers, α-2-biphenylyl-, and α-3-biphenylylbenzyl amine (Table 2).

The best results were obtained with the 2-chloro substituted tosyl imine (**1f**) (59% (for 2 steps) for (**2b**) and 33% for the phenylated amine (**3f**), Table 2, entry 5). Both the 2-iodo (**1b**) and 3-iodo imine (**1c**) also gave the corresponding biphenylphenylmethylamines (**2b**) and (**2c**) in yields of 16 and 21% (2 steps), respectively, with no intermediate products (Table 2, entries 1 and 2, respectively).

We also employed the conditions developed by Fu and co-workers[14] ($Pd(OAc)_2/PCy_3$) with aldimine substrates. Unfortunately, only the aldimines (**1g**) and (**1h**) gave the corresponding target compounds (**2a**) and (**2h**) in over 15% yields (see Supplementary data).

We then decided to screen other catalytic systems, and gratifyingly we observed that the combination of $Pd(dppf)Cl_2/NEt_3$[15] with $NaPh_4B$ as the phenyl transfer reagent, gave better results for the sequential phenylation of activated imines. (**1e**) was transformed cleanly to (**2b**) (92%) (Table 2, entry 12). Likewise, in the case of (**1b**) and (**1j**) these conditions gave selectively the diphenylated target compounds (**2b**) and (**2j**) in 68% and 30% yields, respectively (Table 2, entry 9 and 17).