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Development of a practical and sustainable strategy for the synthesis of ST1535 by an iron-catalyzed Kumada cross-coupling reaction

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ABSTRACT

A simple, convenient, and environmentally friendly route to ST1535 employing an iron-catalyzed cross-coupling reaction and butylmagnesium chloride is described.

Transition metal-catalyzed cross-coupling reactions for the selective formation of C–C bonds enable the preparation of a myriad of structurally diverse and complex molecules that are essential for the development of modern drugs, fine chemicals, materials, and natural products.[1] Palladium- and nickel-catalyzed cross-coupling reactions represent almost all of the C–C bond-forming reactions used in medicinal chemistry today.[2] Thus, every new clinical candidate will require a process-scale implementation of a cross-coupling reaction. The constantly increasing world market price of palladium,[3] the toxicity of nickel compounds,[4] the issue of residual contamination that may affect subsequent transformations and purification, the necessity of extended reaction times in many cases, and the addition of costly and structurally complex ligands are prompting the search for powerful alternatives, especially for industrial processes. The past years have witnessed the development of iron-catalyzed protocols, which boast high operational practicality and synthetic efficiency: the precatalysts are cheap and nontoxic iron salts; complex, air-sensitive ligands are not required; the mild reaction conditions tolerate various functional groups;[5] and even more importantly, the procedures can be applied to nitrogen-rich heterocycles such as purines.[6]

As a part of our ongoing research project on developing new adenosine A_{2A} receptor antagonists as attractive nondopaminergic anti-Parkinson's agents[7] as well as modern/smart procedures for their synthesis,[8] we required the preparation of several small focused library arrays of 2-alkyl-6-amino-9-methyl-8-triazolpurines. Among them, ST1535 is a highly selective adenosine A_{2A} receptor ligand antagonist with an interesting pharmacodynamic profile and might be considered a good clinical candidate for the treatment of Parkinson's disease.[9] Since the preparation of 2-alkyl-substituted 6,8,9-functionalized purine derivatives is not straightforward and limited,[10] we needed to identify a practical and convenient way to access these compounds. Initially, the Stille reaction was used to introduce different alkyl chains at the 2-position of halopurine.[7c] Despite the fact that the Stille reaction was very useful to introduce different alkyl chains at the less reactive 2-position of purine, it showed several drawbacks, including reagents and byproduct toxicity, low turnover number and turnover frequency, harsh reaction conditions (48 h; 120 °C), and problematic final purification. More recently,[8a] we found that 2-halopurines could be efficiently and selectively alkylated by applying a B-alkyl Suzuki–Miyaura cross-coupling reaction in the presence of 3 equiv of Cs_2CO_3 and catalytic $Pd(dppf)Cl_2$ in THF at 60 °C with 2.0 equiv of tri-*n*-alkylborane. A comparative study with other $C(sp^3)$-organometallics and a palladium catalyst revealed that no other organometallics, including *n*-butylboronic acids, could successfully produce the desired product. Furthermore, the reported methodologies do not meet the basic requirements for scale up, and a more sustainable procedure is needed.[11]

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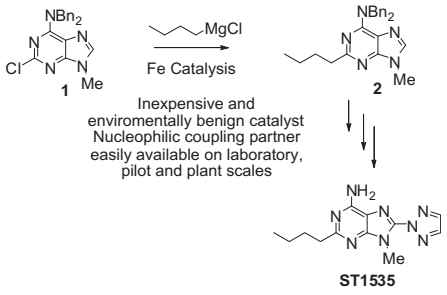
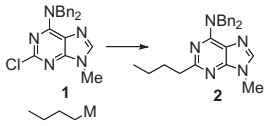
In light of these considerations, we thought it appropriate to report our findings[12] regarding an iron-catalyzed cross-coupling reaction between a 2-chloropurine derivative and butylmagnesium chloride, a key step in the synthesis of ST1535 (Scheme 1).

The reaction of 2-chloropurine **1** (1 mmol) with the *n*-butyl Grignard reagent (1.2 equiv, 2 M in THF) proceeded under mild and practical reaction conditions in the presence of 10 mol % of iron(III) tris(acetylacetonate) [$Fe(acac)_3$] as the precatalyst in THF/NMP (6:1 v/v, 15 mL) at room temperature in 1 h to give **2** in 91% yield of isolated product.[13] Competitive reactions with the alkyl organometallics (e.g., spontaneous decomposition via β-elimination or by proto-demetalation, isomerization or homocoupling) did not occur. The transformation also worked well with a number of alternative iron precatalysts (data not shown), albeit in lower yield than with $Fe(acac)_3$. As $Fe(acac)_3$ is cheap and nonhygroscopic, it is the most appropriate precatalyst in terms of its practicality. While lower catalyst loadings led to slightly reduced yields, the exceptionally low cost of iron and the ease of catalyst removal made the use of 10 mol % loading inconsequential. The absence of NMP and/or THF as well as the use of ligands such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) resulted in longer reaction times and major consumption of Grignard reagent due to decomposition. A 10-fold and 100-fold increase in the reaction scale afforded **2** in 88% and 87% yields of isolated product, respectively. Thus, with coupling product **2** in our hands, an easy, simple synthesis of ST1535 was accomplished using the reported three-step procedure:[7c] (i) regioselective bromination of C8, (ii) bromide displacement with triazole, and (iii) removal of the *N*-benzyl group by TFSA to afford ST1535 in good overall yield. The scope of this iron-catalyzed cross-coupling also includes alkylmagnesium reagents ranging from the small EtMgCl to those bearing longer alkyl chains such as *n*-hexyl and phenethyl.[14] In all cases, levels of conversion were high (>90%) and gave clean products. Lower levels of conversion were seen with the generally less reactive benzyl system.

Comparing the direct butylation using the Grignard reagent with the organoboron- and stannous-based variants shown in Scheme 2, the most prominent features are the short reaction times and very mild reaction temperatures, while still maintaining high yields. Although organomagnesium reagents are highly reactive, the fact that they are easily accessible, among the cheapest of organometallic reagents commercially available on large-scale and have a well-established methodology for safe handling that has contributed to their widespread use in synthetic chemistry is an added benefit of this procedure. Despite the tremendous success of palladium-catalyzed cross-coupling reactions with different nucleophiles, complementary methods that are cheap and mild, avoid toxic waste, and feature improved step- and atom-economy are still highly warranted. The examples shown in Scheme 2 illustrate how, through the use of butylmagnesium reagents, the need to prepare Bu_4Sn or Bu_3B reagents might be avoided, the sometimes notorious problems with purification (complete removal of toxic and nonpolar Sn side products) are eliminated, the amount of waste products is drastically reduced, and excess base (e.g., 3 equiv of Cs_2CO_3) is not required.



Scheme 1. Iron-catalyzed butylation of 2-chloropurine **1**, a key step in the synthesis of ST1535.



Reported method[7c]
M: $SnBu_3$ (MW = 290)
$Pd(PPh_3)_4$ (20 mol%)
NMP, 120 °C, 48 h
79% yield

Reported method[8a]
M: BBu_2 (MW = 124)
$PdCl_2$(dppf) (6 mol%),
Cs_2CO_3 (3 equiv)
THF, 60 °C, 16 h
85% yield

This work
M: MgCl (MW = 59)
$Fe(acac)_3$ (10 mol%)
NMP/THF, r.t., 1 h
91% yield

Scheme 2. Comparison of established methods and the present cross-coupling protocol with organomagnesium chloride reagents and an iron catalyst.

In summary, we have developed a cheaper and more environmentally friendly synthesis of ST1535, a promising molecule for the treatment of Parkinson's disease, using a direct iron-catalyzed cross-coupling of the butylmagnesium chloride reagent and a 2-chloropurine derivative, which are well-known challenging substrates in palladium-mediated cross-coupling chemistry. The cross-coupling reaction takes place under mild conditions with different alkyl Grignard reagents, a short reaction time, and with a reduction of waste. The results from the present study have demonstrated, for the first time, that iron-catalyzed cross-coupling of cheap and readily available alkylmagnesium reagents represents a valuable alternative for the mild, cheap, and atom-economic formation of C–C bonds for the construction of 2-alkylpurines, thus increasing the likelihood that this chemistry could be adopted as an alternative to precious metal catalysis in an industrial setting.

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13. *Synthesis of dibenzyl(2-n-butyl-9-methyl-9H-purin-6-yl)amine:* A flame-dried two-necked flask is charged under argon with *N*,*N*-dibenzyl-2-chloro-9-methyl-9*H*-purin-6-amine **1** (40 g, 0.11 mol), $Fe(acac)_3$ (3.9 g, 0.011 mol), THF (1.4 L), and *N*-methylpyrrolidone (NMP, 220 mL). A solution of *n*-butylmagnesium chloride (2 M in THF, 65 mL, 0.13 mol) is added via syringe to the resulting orange solution, causing an immediate color change to dark brown. The resulting mixture is stirred for 1 h, and the reaction is diluted with AcOEt and is carefully quenched upon the addition of aq HCl (1 M, 300 mL). The phases were separated, and the aqueous phase was further extracted with AcOEt. The combined organic phases were washed with aq HCl (0.1 M, 300 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a residue that was purified by flash chromatography (cyclohexanes–ethyl acetate 7:3), providing the title compound as a colorless oil (38.5 g, 91%). Its analytical and spectroscopic data are in agreement with those published in the literature.
14. *For NMR spectra of ethyl, butyl, phenetyl derivatives see reference* ***7a*** *and* ***8a****:* For hexyl: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J = 8.0 Hz, 3H), 1.34–1.44 (m, 6H), 1.78–1.92 (m, 2H), 2.87 (t, J = 8 Hz, 2H), 3.79 (s, 3H), 4.95 (br, 2H), 5.53 (br s, 2H), 7.32 (s, 10H), 7.66 (s, 1H); MS (ESI) 414 $(M+1)^+$.