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Copper-Catalysed α-Selective Allylic Alkylation of Heteroaryllithium Reagents

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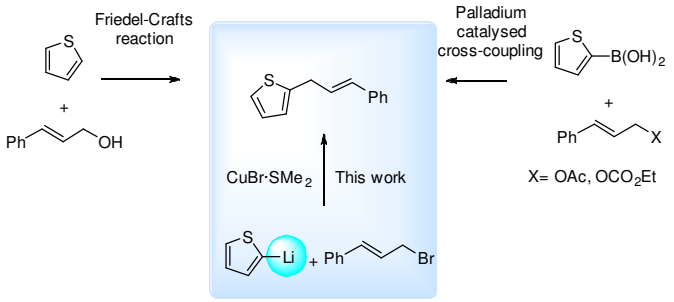
2-Allyl-substituted thiophenes and furans are synthesised efficiently in a direct procedure using 2-heteroaryllithium reagents and allyl bromides and chlorides catalysed by ligand-free copper (I). The reactions take place under mild conditions, with excellent α-selectivity, high functional group tolerance and good yields for the S_N2 products.

Introduction

Heteroarenes such as thiophene and furan have attracted great attention in the last decades, due to their versatility in synthesis and specific properties.[1] These heterocyclic compounds have been used extensively in material science for organic dyes and electronic devices,[2] in agriculture and pharmaceutical chemistry[3] or as intermediates for the synthesis of natural products or flavours.[4] Therefore, the functionalization of furans and thiophenes at C2 represents an important target for organic synthesis.[1] In this context, the allylic substitution is a very convenient reaction,[5] due to the fact that the incorporated olefin motif may serve as a latent group for further transformations. There are a number of methods for allylic substitutions with heterocycles (Scheme 1). For example, the Friedel-Crafts[6] reaction represents a straightforward manner to access to 2-allylheteroarenes, but usually this transformation suffers from a lack of regioselectivity, both in the heteroarene and in the allyl electrophile, especially when thiophene is used as a nucleophile.[7] On the other hand, several successful cross-coupling reactions catalysed by palladium[8] and copper[9] have been described, but in these cases a pre-functionalised thiophene or furan is needed. Usually, a boronic, organotin or organosilicon reagent is used in these cross-coupling reactions. As part of our continuing efforts to employ organolithium[10] reagents in asymmetric allylic substitutions[11] and palladium cross-coupling reactions,[12,13] we were interested in the direct allylic alkylation of 2-heteroaryl lithium reagents. Herein, we present an α-selective allylic alkylation of 2-heteroaromatic lithium reagents using copper as a catalyst.[14] In this way, the initial functionalization of the organometallic reagent is avoided, wich allows the synthesis of 2-allyl-substituted heterocycles in an efficient and straightforward procedure.



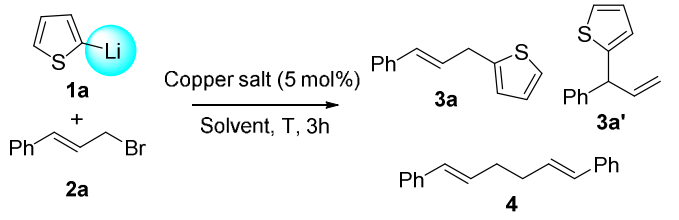
Scheme 1 Different methodologies for allylic alkylation of thiophene.

Results and discusion

Our studies began with the reaction of the 2-thienyllithium[15] and cinnamyl bromide, both commercially available. Different solvents, temperatures and copper sources were evaluated (Table 1). Initially, solvents such as toluene, TBME and THF (entries 1-3, respectively), using CuBr·SMe_2 as a catalyst at -80 °C, were tested. Gratifyingly, full conversion and complete S_N2 selectivity (99:1, linear:branched) was achieved when THF was used as a solvent. This copper (I) catalysed allylic

alkylation reaction shows high regioselective to the α-substituted product, independently of the absence or presence of a ligand.[16] Importantly, when copper(I) was not used the conversion dropped significantly (entry 4). We decided for practical reasons to carry out the reaction at higher temperature, therefore the allylic alkylation was tested at 0 °C. A screening of different copper (I) salts (entries 5-7) revealed that CuBr·SMe_2 is the most efficient catalyst for this transformation. When the reaction was run at 0 °C, a small amount of homocoupling product **4** was still formed (entry 5). Finally, when the reaction was performed at -5 °C in THF and using CuBr·SMe_2, full conversion was achieved (86% isolated yield of **3a**) without the presence of product **4**. When the reaction was carried out at room temperature, a complex mixture was obtained and the ^{1}H NMR of the crude mixture was difficult to analyse. Interestingly, when cinnamyl chloride was used (entry 12, table 1), full conversion and high regioselectivity to the linear product were also observed and the corresponding product **3a** was obtained in 93% yield.

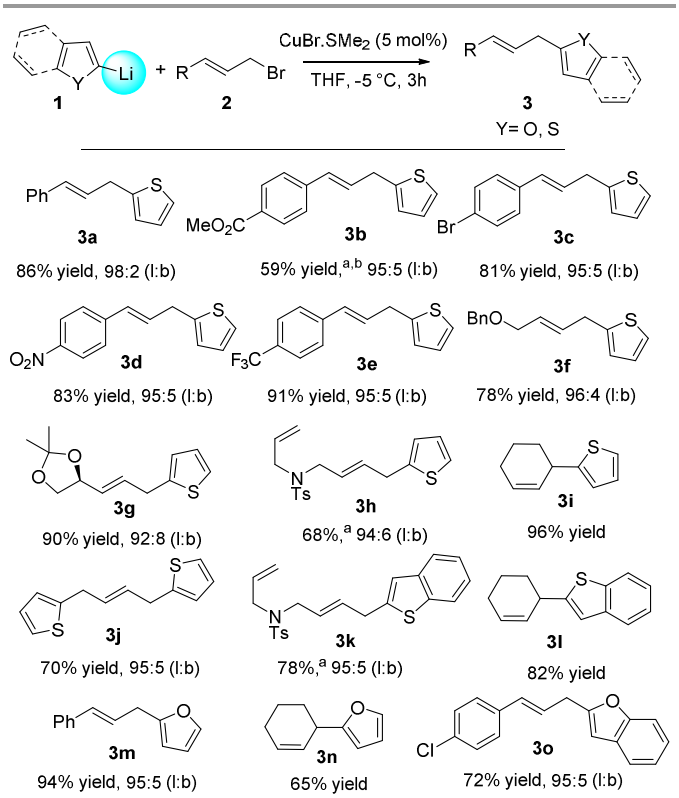
Table 1 Optimization of the reaction conditions.[a]



Entry	Solvent	copper	T (°C)	Conv.[b] (%)	**3a+3a'**[b] (l:b)[c] (yield)[d]	**4** (%)[b]
1	Toluene	CuBr·SMe_2	-80	95	90% (99:1)	5
2	TBME	CuBr·SMe_2	-80	90	80% (99:1)	10
3	THF	CuBr·SMe_2	-80	Full	Full (99:1)	0
4	THF	-	-80	35	25% (99:1)	10
5	THF	CuBr·SMe_2	0	Full	94% (97:3)	6
6	THF	CuCl	0	55	50% (98:2)	5
7	THF	CuI	0	80	60% (98:2)	20
8	THF	-	0	80	60% (98:2)	20
9	THF	CuBr·SMe_2	-5	Full	Full (98:2) (86%)	0
10[e]	THF	CuBr·SMe_2	-5	Full	Full (98:2) (93%)	0

[a] Reaction conditions: copper salt (0.01 mmol, 5 mol%), 1.5 eq. of **1a** and 0.2 mmol of **2a** in 2 mL of solvent. [b] Conversions were determined by ^{1}H NMR. [c] linear:branched ratio was determined by GC. [d] Isolated yield after column chromatography. [e] cinnamyl chloride was used as a allylic reagent.

With the optimised conditions in hand (Table1, entry 9), the scope of this reaction was investigated (Scheme 2). It should be emphasized that high functional group tolerance was observed and cinnamyl bromides with different substituents, such as methyl ester, bromide,[17] NO_2 or CF_3 groups in *para* position at the aromatic ring can be present, affording the corresponding products **3b-3e**, in good to high yields with excellent levels of regioselectivity. Other functional groups such as benzyl ether or a dioxalane ring were allowed and the corresponding products **3f** and **3g**, were obtained in 78 and 90% yield, respectively. Also, the presence of N-Ts-protected amines was tolerated, but in this case 1.1 eq. of organolithium reagent was used in order to obtain good yield. Furthermore, multiple coupling of **1a** is shown in the twofold alkylation of (*E*)-1,4-dibromobut-2-ene, providing the corresponding dialkylated product **3j** in 70% isolated yield. Next, different heteroaryllithium reagents were tested. For example benzo[b]thiophen-2-yllithium, easily prepared by direct metallation with *n*-BuLi,[18] was successfully coupled with (*E*)-*N*-allyl-*N*-(4-bromobut-2-en-1-yl)-4-methylbenzenesulfonamide and 3-bromocyclohexene, affording the corresponding products **3k** (78%) and **3l** (81%) in high yields. 2-Furanyllithium and 2-benzofuranyllithium, freshly prepared by direct metallation, were also suitable partners for this reaction, resulting in products **3m-3o**, with high regioselectivity and good yields.



Scheme 2 Scope of copper(I)-catalysed allylic alkylation. Reaction conditions: allyl bromide **2** (0.2 mmol) was added to a stirred solution of CuBr·SMe_2 (0.01 mmol) in 2 mL of dry THF at -5 °C; 2-heteroaryllithium reagent **1** (0.3 mmol) was added dropwise over 1h. Isolated yield after column chromatography. Linear:branched ratio determined by GC. [a] 1.1 eq. of 2-heteroaryllithium reagent **1** was used. [b]1,2-addition to the carbonyl group was also observed as a side reaction.

Conclusions

In summary, we have developed a highly regioselective ligand-free copper(I) catalysed allylic alkylation using directly 2-heteroarylithium reagents. The corresponding α-substituted products are obtained in good to excellent yields (up to 94%). The reaction takes place under mild conditions and tolerates a wide range of functional groups and offers a method for direct access to various C2-substituted heterocycles.

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15 Comparison of commercially available 2-thienyl organometallic reagents (source: Sigma-Aldrich (2014)): 2-thienyllithium solution (1M) =690 €/mol; (2-thienyl)trimethylsilane= 1300 €/mol; 2-(tributylstannyl)thiophene= 1330 €/mol; 2-thienylboronic acid= 3350 €/mol; 2-thiopheneboronic acid MIDA ester= 5970€/mol.

16 Different phosphine based ligands such PPh_3, 1,3-bis(diphenylphosphanyl)propane, (rac)-BINAP, (*R*,*R*)-Taniaphos, (*R*,*S*)-Josiphos were tested and in all cases highly regioselectivity to the α-substituted product was observed.

17 No dehalogenation was observed in the course of the reaction for the (*E*)-1-bromo-4-(3-bromoprop-1-en-1-yl)benzene.

18 See supporting information for further details.