This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Copper-Catalysed \(\alpha\)-Selective Allylic Alkylation of Heteroaryllithium Reagents

Carlos Vila, Valentín Hornillos, Martín Fañanás-Mastral and Ben L. Feringa

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 \(\alpha\)-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.\(^5\) In this context, the allylic substitution is a very convenient reaction,\(^6\) 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-allyl heteroarenes, 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 \(\alpha\)-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, which allows the synthesis of 2-allyl-substituted heterocycles in an efficient and straightforward procedure.

Results and discussion

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) catalyst...
alkylation reaction shows high regioselective to the α-substituted product, independently of the absence or presence of a ligand. 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·SMe₂ 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·SMe₂, 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 ¹H 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>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Copper</th>
<th>T (°C)</th>
<th>Conv. (％)</th>
<th>3a+3a′ (％)</th>
<th>4 (％)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>CuBr·SMe₂</td>
<td>-80</td>
<td>95</td>
<td>90% (99:1)</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>TBME</td>
<td>CuBr·SMe₂</td>
<td>-80</td>
<td>90</td>
<td>80% (99:1)</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>CuBr·SMe₂</td>
<td>-80</td>
<td>Full</td>
<td>Full (99:1)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>-</td>
<td>-80</td>
<td>35</td>
<td>25% (99:1)</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>CuBr·SMe₂</td>
<td>0</td>
<td>Full</td>
<td>94% (97:3)</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>CuCl</td>
<td>0</td>
<td>55</td>
<td>50% (98:2)</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>Cu</td>
<td>0</td>
<td>80</td>
<td>60% (98:2)</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>-</td>
<td>0</td>
<td>80</td>
<td>60% (98:2)</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>CuBr·SMe₂</td>
<td>-5</td>
<td>Full</td>
<td>Full (98:2) (86%)</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>CuBr·SMe₂</td>
<td>-5</td>
<td>Full</td>
<td>Full (98:2) (93%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* 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. Conversions were determined by ¹H NMR. Linear:branched ratio was determined by GC. Isolated yield after column chromatography. Cinnamyl chloride was used as an alkylic reagent.

With the optimised conditions in hand (Table 1, 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, nitro or CF₃ 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-ylithium, easily prepared by direct metallation with n-BuLi, 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·SMe₂ (0.01 mmol) in 2 mL of dry THF at 5 °C; 2-heteroaryllithium reagent 1 (0.3 mmol) was added dropwise over 1 h. Isolated yield after column chromatography. Linear:branched ratio determined by GC. 1.1 eq. of 2-heteroaryllithium reagent 1 was used. 4-L,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-heteroaryllithium 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.
Acknowledgements

Financial support from The Netherlands Organization for Scientific Research (NWO-CW), National Research School Catalysis (NRSC-Catalysis), the European Research Council (ERC advanced grant 227897), the Royal Netherland Academy of Arts and Sciences (KNAW) and the Ministry of Education Culture and Science (Gravity program 024.601035) is gratefully acknowledged. C.V. was supported by Intra-European Marie Curie fellowship (FP7-PEOPLE-2011-IEF-300826). We thank T. D. Tiemersma-Wegman for the HRMS analysis.

Notes and references

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands. Fax: +31 50 363 4278; Tel: +31 50 3634296; E-mail: b.l.feringa@rug.nl.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/


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

16 Different phosphate based ligands such PPh3, 1,3-bis(diphenylphosphinyl)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.