Re-orienting coupling of organocuprates with propargyl electrophiles from $S_N2'$ to $S_N2$ with stereocontrol†

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Diorganocuprate(I) reagents derived from lithiated heterocycles and CuCN react with enantioenriched secondary propargyl bromides to give the corresponding propargylated heterocycles. While propargyl electrophiles typically undergo $S_N2'$ displacement, this transformation represents the first example of the reaction of hard carbanions with propargyl electrophiles in an $S_N2$ fashion and occurs with excellent levels of stereoinversion. The new method was applied to the formal synthesis of (+)-frondosin B.

Nucleophilic organocuprate(I) reagents are unambiguously invaluable synthetic tools for the chemo-, regio- and stereo-selective delivery of hard carbanions in a number of transformations such as carbocuprations, alkenylations or allylations. Regio- and stereo-selective organocuprate(I) mediated substitutions of allylic electrophiles have been successfully developed to obtain either the $S_N2$ or $S_N2'$ adduct (eqn (a)). In contrast, substituted propargylic electrophiles are only known to react in an $S_N2'$ fashion to form the corresponding allene, regardless of the nature of the leaving group ($R^2$ or $R^3 \neq H$, eqn (b)). Fu has pioneered a direct $S_N2$ substitution of propargyl electrophiles by developing enantioselective nickel-catalyzed Negishi cross-couplings of propargyl bromides and carbonates with aromatic organozinc reagents (eqn (c)). However, the reactions with heteroaromatic nucleophiles have not been reported to date. Furthermore, in our hands, attempts to apply Fu’s protocol to heterocyclic nucleophiles did not prove efficacious. The ubiquity of bioactive compounds bearing at least one heterocycle encouraged us to delineate a complementary protocol allowing the use of heteroaromatic nucleophiles that would solve this unanswered synthetic problem. Thus, we wondered whether a heteroaryl organocopper(I) reagent could be directed to react with propargyl electrophiles in an $S_N2$ rather than the known $S_N2'$ mode (eqn (d)).

At the outset of our study, based on current knowledge about reaction mechanisms involving nucleophilic organocuprate(I) reagents, we considered the mechanistic manifold depicted in Scheme 1 as a working hypothesis. We reasoned that the $S_N2'$ selectivity observed for reactions between organocuprate(I) reagents and propargyl electrophiles may be explained by the first step of the mechanism where coordination of the copper

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Scheme 1 Proposed rationale for the formation of allenes.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6sc01086e
formation of the desired \( \text{S}_2 \text{O} \text{adduct} \) (Scheme 1, bottom). Such a distinction may occur by adjusting the HOMO–LUMO energies since \( \pi \)-coordination requires favorable interactions with both the HOMO and the LUMO of the copper(II) complex while oxidative addition into the \( \text{C}_\text{a} \text{–LG} \) only involves interaction with the HOMO. In practice, we anticipated that this differentiation could be achieved using coordinatively saturated organocuprates(i). The targeted transformation is nevertheless very challenging since, after oxidative addition into the \( \text{C}_\text{a} \text{–LG} \) bond, the propargycopper(iii) species generated could rapidly isomerize to the arguably more stable allenycopper(iii). This would ultimately result in the formation of the undesired \( \text{S}_2 \text{O} \text{allene product and/or racemization (Scheme 1).} 

With these considerations in mind, we began to explore the targeted reaction using furan \( 1 \text{a} \) in which the pendant alcohol would serve both as a directing group for site selective deprotonation and as a chelating group to saturate the coordination sphere of the copper. Previous studies on the displacement of aliphatic electrophiles with nucophile organocopper(i) reagents suggest that the \( \text{S}_2 \text{O} \) reaction is more efficient in a polar solvent.\(^5\) Our investigation thus started by identifying the preferred leaving group using DME as a solvent and CuCN as the copper(i) salt (Table 1, entries 1–7). Commonly used leaving groups in the \( \text{S}_2 \text{O} \) displacement of propargyl electrophiles with organocopper(i) nucleophiles gave disparate results, both in terms of reactivity and selectivity. Thus, propargyl sulfonates were found to be superior substrates compared to propargyl phosphates to achieve the desired transformation (entries 1 and 5 versus 2 and 6). Aryl sulfonates and phosphates are more reactive than their aliphatic counterparts (entries 1 and 2 versus 5 and 6). Interestingly, the observed regioselectivity seems to depend upon the nature of the leaving group (entries 1 to 6). The use of a perfluoroalkylated ester introduced by Dieter et al.\(^6\) resulted in partial conversion of the starting electrophile and formation of the desired product \( 2 \text{a} \) in moderate yield and selectivity (entry 4). In addition, a Troc leaving group performed poorly leading to a complex mixture with no desired product observed (entry 3). We then became intrigued about the possibility of using a bromide as leaving group. We found that a bromide acts as a good leaving group but also greatly impacts the selectivity towards the formation of the desired alkyne \( 2 \text{a} \) (entry 7). Various copper(i) salts were also rapidly surveyed and, amongst others, CuI was found to be as efficient as CuCN albeit with a drop in selectivity (entries 8 versus 7). On the other hand, CuSPh failed to deliver the desired alkyne (entry 9).

Since the nature of the solvent is known to possess a strong effect on reactivity and selectivity in organocopper(i) chemistry, we evaluated alternative solvents. Running the displacement reaction in THF produced \( 2 \text{a} \) in diminished yield and selectivity. Conversely, using \( \text{Et}_2\text{O} \) as a solvent resulted in the absence of reactivity (entry 11). Whitesides and co-workers previously observed that \( \text{Et}_2\text{O} \) as a solvent can negatively impact the reactivity of organocopper(i) reagents towards alkyl electrophiles.\(^7\) Not surprisingly, reacting the organolithium reagent with the propargyl bromide in the absence of copper(i) salt resulted in the degradation of the reactants (entry 12).

With optimized conditions for controlling the regioselectivity of the heterocycle transfer (entry 7), we initiated the study of the enantioselectivity of the reaction by developing a facile synthesis of previously inaccessible enantioenriched propargyl bromides \( 4 \). These are readily obtained in high yields via highly enantioselective Noyori reduction of ynone \( 3 \) followed by the one-pot activation and displacement of the alcohol in the presence of commercially available bromo(triphenyl) phosphonium bromide (Scheme 2).\(^8\) Noteworthy, under these conditions, the bromide substitution reactions occur with high levels of inversion of configuration. To our delight, under the conditions previously established (Table 1, entry 7), the reaction of the diorganocuprate(i) derived from \( 1 \text{a} \) with \( \text{S}^\text{2} \text{(-3-bromohex-1-yn-1-yl)methylisilane 4a (98% ee) delivered (R)-2a in 96% ee and a re-producible 77% yield. Further extension to a variety of enantioenriched propargyl bromides 4 was conducted to deliver enantioenriched propargyl heteroaoyls 2 in good yields and with good levels of stereoinversion.}

Our study focused on diorganocuprates derived from readily accessible x-lithiated heterocycles obtained via direct lithiation of the corresponding heterocycles. The results, compiled in Fig. 1 demonstrate the generality of the method. We initially observed that a carboxylate may be used in place of the alkoxide as a directing group without losing selectivity (example 2c). We

**Table 1** Selected optimization studies

| Entry | Leaving group | Solvent | \( 2 \text{a}/\text{2b} \) | % conv.\(^a\) | % yield\(^b\) |
|-------|--------------|---------|----------------|----------------|----------------|
| 1     | OMs          | DME     | 70 : 30        | 82             | 44             |
| 2     | OP(O)(OEt)\(_3\) | DME     | 90 : 10        | 42             | 27             |
| 3     | OTrc         | DME     | n.d.           | 0              | 0              |
| 4     | OCO\(_2\)F\(_2\) | DME     | 71 : 29        | 66             | 22             |
| 5     | OSO\(_3\)Ph | DME     | 75 : 25        | 100            | 61             |
| 6     | OP(O)(OPh)\(_2\) | DME     | 74 : 26        | 100            | 58             |
| 7     | Br           | DME     | 94 : 6         | 100            | 77             |
| 8\(^b\) | Br         | DME     | 89 : 11        | 100            | 68             |
| 9\(^\circ\) | Br         | DME     | —              | 100            | 0              |
| 10    | Br           | THF     | 82 : 18        | 100            | 63             |
| 11    | Br           | \text{Et}_2\text{O} | —              | 0              | 0              |
| 12\(^d\) | Br         | DME     | —              | 0              | 0              |

\(^a\) All reactions were performed on 0.5 mmol scale using CuCN (0.5 mmol). \(^b\) The reaction was run using CuI (0.5 mmol). \(^\circ\) The reaction was run using CuSPh (0.5 mmol). \(^d\) The reaction was performed in the absence of copper(i) salts.

**Scheme 2** Synthesis of enantioenriched propargyl bromides.
In addition, this stereo-selective displacement is also efficient when the starting bromide 4 possess a secondary center adjacent to the reactive carbon center such as an iso-propyl group (2g). Overall, the scope of the transformation compares favorably to the Negishi cross-couplings developed by Fu. As illustrated in Fig. 1, both enantiomers are of equal ease to access using our strategy and the levels of enantioselectivity achieved are good. Furthermore, while the reactions were routinely run on a 1 mmol scale, we successfully utilized our protocol on up to 50 mmol scale.

As nicely highlighted in Jarvo and co-workers’ recent work, in the context of drug discovery, the strategic introduction of a methyl group can improve drug potency through various mechanisms in the hit to lead approach. It is thus interesting to observe that tertiary benzylic stereocenters bearing a methyl group are common motifs in medicines. In particular, such a motif is present in a number of heteroaromatic bioactive compounds with varied activities (Fig. 2). Development of stereoselective methods to obtain these compounds are relevant both from a synthetic and a practical point of view since the different enantiomers are known to possess differential bioactivity. In addition, methods to access these motifs are still scarce. We decided to probe further the scope of the transformation towards the synthesis of such privileged building blocks. Example 2j and 2m (Fig. 1), already hinted to the possibility of using our newly designed strategy for their synthesis.

Interestingly, molecular complexity may be rapidly built by combining our displacement reaction with other transformations. As shown in Scheme 3, methyllithium can be added to 3-furan-carboxaldehyde and the corresponding alkoxide can be used as a directing group for metatation. In spite of the proximal presence of the racemic alkoxide, no effect on the enantioselectivity was observed. Thus, transmetallation to CuCN and treatment with (S)-(3-bromobut-1-yn-1-yl)trimethylsilane 4b followed by Dess–Martin oxidation of the corresponding alcohol 2n delivered the doubly functionalized methylketone 5a in 68% yield and 95% ee. Alternatively, we found that the displacement reaction is selective for propargyl bromides over other electrophiles that can in turn be functionalized. Thiophene 2o, was obtained using this strategy. This approach allows for further functionalization of the S_n2 adduct via the subsequent transformation of the sulfonate as illustrated by the preparation of azide 5b (Scheme 3). The selectivity of the displacement reaction for the propargyl bromide over other electrophiles such as primary alkylchlorides and arylsulfonates is particularly noteworthy. Indeed, even secondary alkylhalides and arylsulfonates are known to undergo S_n2

![Fig. 1 Scope of the copper-mediated displacement.](image1)

![Fig. 2 Bioactive compounds with a benzyl methyl group.](image2)
displacement with diorganoocuprate(I) reagents at low temperatures.\textsuperscript{14}

Having established this methodology, we wanted to demonstrate its potential for natural product synthesis. The synthetic utility of the novel displacement was thus further demonstrated by the rapid assembly of aldehyde 5c that was used as a key intermediate in the synthesis of (+)-frondosin B.\textsuperscript{15}

Thus, applying our protocol, alkyne 2p was obtained in 79% yield, 96% ee and with full $S_n 2$ selectivity. Deprotection of the TMS-alkyne with TBAF/AcOH followed by hydroboration and oxidation of the intermediate vinylborane, delivered the targeted enantioenriched aldehyde 5c in good yield over 3 steps, completing the formal synthesis of (+)-frondosin B (Scheme 4). The absolute configuration of intermediate 5c was confirmed by measurement of its specific rotation, which was comparable to the value obtained previously.\textsuperscript{15} This means that the displacement occurs with Walden inversion at the electrophilic carbon bearing the bromide.\textsuperscript{16}

While the origin of the observed $S_n 2$ selectivity and high stereoinversion have not yet been elucidated, a scenario in which: (i) the diorganoocuprate(I) oxidatively adds into the C$_2$-Br bond and (ii) the resulting copper(II) species is undergoing rapid reductive elimination is plausible. In this context, it also worth noting that our attempt to react diarylocuprate(I) nucleophiles with propargyl bromides 4a was poorly regioselective and resulted in the obtention of mixtures of the desired alkynes together with allenes.\textsuperscript{2,17} These additional observations suggest that the presence of the heteroatom $z$- to the copper center is important to achieve the desired selectivity. In 2012, Nakamura published guidelines for the structure/reactivity relationship of nucleophilic organocuprate(I) reagents based on orbital analysis.\textsuperscript{6} Following this analysis, a linear geometry at copper would inhibit alkyne coordination and favor oxidative addition into the C$_2$-Br bond (Scheme 5). The presence of lithium cations could additionally increase the rate of oxidative addition into the C$_2$-Br bond by coordination of the lithium to the bromine atom.\textsuperscript{18} Overall, we propose that the high affinity of the heteroatoms (O, S, N) for lithium invoked to explain the behavior of “dummy” ligands,\textsuperscript{19} might favor the linear geometry for the diorganoocuprate(I) intermediates and would ultimately account for the observed reactivity. A putative simplified structure for the diheteroarylcuprate(I) reagents is distorted square planar (Scheme 5). It is also interesting to note that, in the case of adduct 2f, the organo-cuprate resulting from oxidative addition undergoes reductive elimination faster than the Kociěński style migratory insertion.\textsuperscript{20}

In summary, we have developed the first example of a selective $S_n 2$ displacement of propargyl electrophiles with hard carbonions employing readily accessible diorganoocuprate(I) reagents and enantioenriched propargyl bromides. This transformation is particularly selective with heterocyclic nucleophiles, occurs with stereoinversion at the C$_2$sp$^2$ center, and leads to versatile enantioenriched allenes. The success of the copper mediated reaction in generating highly enantiomerich propargylic centers represents a useful complement to the nickel-catalyzed protocol that failed when attempted using the reported optimized conditions. In addition, the reaction scope compares favorably to the nickel catalyzed Negishi coupling. The synthetic utility of this novel transformation was illustrated by a short formal synthesis of (+)-frondosin B. We expect this transformation to offer new synthetic opportunities not hitherto conceivable. Extension of this method to other types of nucleophiles and in particular to standard aromatic nucleophiles is underway and will be reported in due course.

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