Organic Chemistry |Hot Paper|

# Diastereo- and Enantioselective Cross-Couplings of Secondary Alkylcopper Reagents with 3-Halogeno-Unsaturated Carbonyl Derivatives

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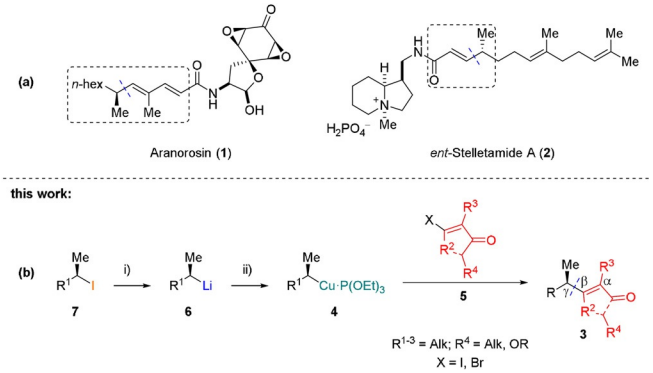
**Abstract:** Chiral secondary alkylcopper reagents were prepared from the corresponding alkyl iodides with retention of configuration by an I/Li-exchange using *t*BuLi (−100 °C, 1 min) followed by a transmetalation with CuBr·P(OEt)$_3$ (−100 °C, 20 s). These stereodefined secondary alkylcoppers underwent stereoretentive cross-couplings with several 3-iodo or 3-bromo unsaturated carbonyl derivatives leading to the corresponding γ-methylated Michael acceptors in good yields and with high diastereoselectivities (dr up to 96:4). The method was extended to enantiomerically enriched alkylcoppers, providing optically enriched advanced natural product intermediates with up to 90% *ee*.




**Scheme 1.** Natural products bearing a chiral center vicinal to an α,β-unsaturated carbonyl derivative (a). Cross-couplings of chiral alkylcopper reagents with 3-halogeno-unsaturated carbonyl derivatives (b). i) *t*BuLi (inv. add., 2.2 equiv), pentane/ether (3:2), −100 °C, 1 min, ii) CuBr·P(OEt)$_3$ (in ether, 2.0 equiv) −100 °C, 20 s.

α,β-Unsaturated carbonyl derivatives are valuable synthetic intermediates[1] and are present in various natural products such as aranorosin (**1**)[2] or *ent*-stelletamide A (**2**)[3] (see Scheme 1 a). For example, Landis et al.[4] reported a one-pot protocol involving an iterative asymmetric hydroformylation and subsequent Wittig olefination for the preparation of such γ-chiral α,β-unsaturated carbonyls. Alternatively, chiral molecules of type **3** may be prepared by the retentive cross-coupling of α-chiral organometallic reagents (**4**) with 3-halogeno-unsaturated carbonyl derivatives of type **5**.

Recently, we have reported the preparation of chiral secondary alkyllithium reagents **6**, which were readily prepared from the corresponding alkyl iodides **7** via a stereoretentive I/Li-exchange reaction performed in a mixture of pentane:ether (3:2) at −100 °C using *t*BuLi. (see Scheme 1 b).[5] Subsequent transmetalation of these secondary alkyllithium intermediates with CuBr·P(OEt)$_3$ afforded the corresponding secondary alkylcopper reagents **4**, which were configurationally stable in THF at −50 °C for several hours.[6] Herein, we wish to report stereoselective cross-couplings of chiral alkylcopper reagents (**4**) with a range of 3-halogeno Michael acceptors of type **5** leading to γ-methylated α,β-unsaturated carbonyl derivatives of type **3**. (see Scheme 1 b).

In preliminary experiments we have treated the diastereomerically pure alkyl iodide *syn*-**7a**[5c] with *t*BuLi (2.2 equiv) in a 3:2 mixture of pentane:diethyl ether at −100 °C for 1 min followed by a dropwise addition of CuBr·P(OEt)$_3$ solution (2.0 equiv, 3 M in ether) leading to the corresponding alkylcopper reagent *syn*-**4a** (see Table 1).

Such chiral secondary alkylcoppers were known to be configurationally stable at −50 °C in THF,[6] therefore we have removed the solvents by vacuum and have replaced it with THF. Next, we have investigated this cross-coupling with various cyclopentenone derivatives bearing a leaving group at position 3. Therefore, cyclopentane-1,3-dione was converted into the corresponding tosylate (**5a**),[7a] triflate (**5b**)[7b] and pentafluorobenzoate (**5c**).[7c] Thus, we have noticed that the reaction of *syn*-**4a** with the electrophiles **5a–c** did not afford any product of type **3** even after stirring for 12 h at −50 °C. However, the reaction of *syn*-**4a** with 3-iodocyclopent-2-en-1-one (**5d**)[8] afforded the desired product *syn*-**3a** in 35% yield with dr = 93:7.

Better results were obtained with 3-bromocyclopent-2-en-1-one (**5e**)[9] as substrate and addition thereof to a solution of *syn*-**4a** provided the cyclopentenone *syn*-**3a** in 62% yield with dr = 92:8 (entry 5).

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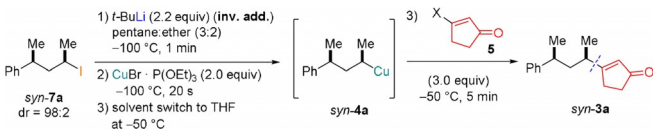
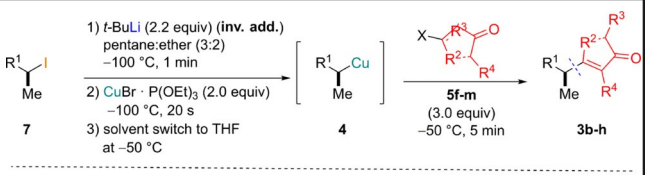
**Table 1.** Determination of appropriate electrophiles for the stereoretentive cross-coupling of *syn*-**4a** with electrophiles of type **5** affording the cyclopentenone derivative *syn*-**3a**.




| Entry | Cyclopentenone derivative **5** | Yield of *syn*-**3a**[a] | dr of *syn*-**3a**[b] |
|---|---|---|---|
| 1 | **5a**: X = OTs | no product[c] | – |
| 2 | **5b**: X = OTf | traces[c] | – |
| 3 | **5c**: X = $OC(O)C_6F_5$ | traces[c] | – |
| 4 | **5d**: I | 35% | 93:7 |
| 5 | **5e**: Br | 62% | 92:8 |

[a] Yield of analytically pure products. [b] The diastereomeric ratio (dr, *syn*/*anti* ratio) was determined by $^1$H and $^{13}$C NMR analysis. [c] No product was obtained even after a reaction time of 12 h at −50 °C.

**Table 2.** Stereoretentive preparation of secondary alkylcopper reagents **4** and trapping with α,β-unsaturated carbonyl derivatives of type **5** leading to γ-methylated Michael acceptors of type **3**.



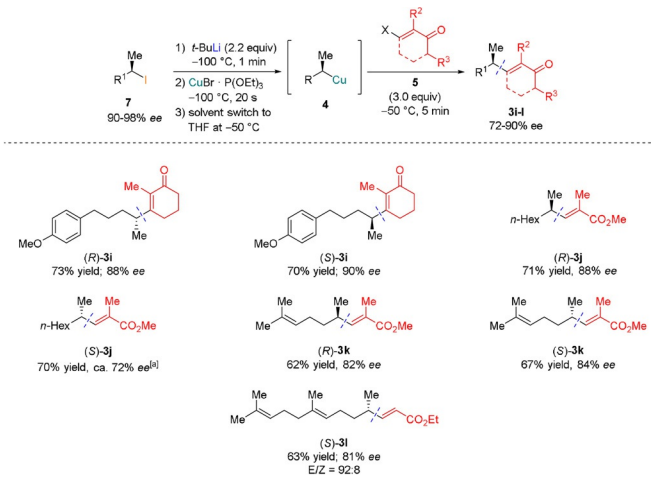

| Entry | Alkylcopper | Electrophile | Product of type 3 |
|---|---|---|---|
| 1 | *syn*-**4a** | **5f**: X = I<br>**5g**: X = Br | *syn*-**3b**<br>X = I: 66%yield; dr = 94:6<br>X = Br: 49% yield; dr = 96:4 |
| 2 | *syn*-**4a** | **5h** | *syn*-**3c**:<br>77% yield; dr = 96:4 |
| 3 | *syn*-**4a** | *Z*-**5i** X = I<br>*Z*-**5j** X = Br | *syn*-**3d**<br>X = I: 81% yield; dr = 96:4<br>X = Br: 65% yield; dr = 93:7 |
| 4 | *syn*-**4a** | *Z*-**5k** | *syn*-**3e**<br>49% yield; dr = 94:6 |
| 5 | *syn*-**4a** | *E*-**5l** X = I<br>*E*-**5m** X = Br | *syn*-**3f**<br>X = I: 77% yield; dr =94:6<br>X = Br: 45% yield; dr = 80:20 |
| 6 | *syn*-**4b** | *Z*-**5i** | *syn*-**3g**<br>73% yield; dr = 95:5 |
| 7 | *anti*-**4b** | *Z*-**5i** | *anti*-**3g**<br>81% yield; dr = 5:95 |
| 8 | *syn*-**4c** | *Z*-**5i** | *syn*-**3h**<br>37% yield; dr = 96:4 |
| 9 | *anti*-**4c** | *Z*-**5i** | *anti*-**3h**<br>44% yield; dr = 9:91 |

[a] Yield of analytically pure products. [b] The diastereomeric ratio (dr, *syn*:*anti* ratio) was determined by $^1$H NMR, $^{13}$C NMR or GC-analysis. [c] The depicted relative stereochemistry of the major stereoisomer is only presumed on the basis of previous studies.[5,6]

With these results in hand, we have performed the stereoselective cross-coupling of *syn*-**4a** with a range of 3-halogeno Michael acceptors of type **5** (see Table 2). Thus, 3-iodo- and 3-bromocyclohexenone (**5f** and **5g**)[10] reacted smoothly with *syn*-**4a** leading to *syn*-**3b** in 49–66% yield with dr > 94:6 (entry 1). Similarly, the cross-coupling of *syn*-**4a** with 3-iodo-2-methyl cyclohexenone (**5h**)[12] as electrophile afforded *syn*-**3c** in 77% yield with dr = 96:4 (entry 2). Furthermore, we have treated several 3-iodo or 3-bromo acrylates (**5i**–**5m**)[12–14] with diastereomerically enriched alkylcoppers of type **4**. Therefore, the coupling of *syn*-**4a** with either (*Z*)-ethyl 3-iodo-acrylate (*Z*-**5i**) or with (*Z*)-ethyl 3-bromo-acrylate (*Z*-**5j**) furnished stereoselectively *syn*-**3d** in 65–81% yield with dr up to 96:4 (*E*:*Z* > 1:99, entry 3). Furthermore, the (*Z*)-ethyl enoate *syn*-**3e** was prepared in 49% yield (dr = 94:6, *E*:*Z* > 1:99, entry 4). The cross-coupling of *syn*-**4a** with either *E*-**5l** or *E*-**5m** provided the unsaturated ester *syn*-**3f** in 45–52% yield with moderate diastereoselectivity (dr > 80:20, entry 5). To our delight, we could expand this cross-coupling to other secondary alkylcopper reagents (*syn*- and *anti*-**4b**-**c**)[5b,d] with the iodenoate (*Z*-**5i**) (entries 6–9). Thus, the reaction of the secondary alkylcopper reagent *syn*-**4b** with (*Z*)-**5i** afforded the corresponding α,β-unsaturated ester *syn*-**3g** in 73% yield and dr = 95:5 (entry 6). The corresponding *anti*-alkylcopper reagent *anti*-**4b** was prepared and subsequent cross-coupling with (*Z*)-**5i** afforded *anti*-**3g** in 81% yield and dr = 5:95 (entry 7). In addition, the OTBS-substituted Michael acceptors *syn*-**3h** (37% yield, dr = 94:6, entry 8) and *anti*-**3h** (44% yield, dr = 9:91, entry 9) were readily prepared.

We were able to further extend this method to the functionalization of optically enriched secondary alkyl iodides.[6b] For example, (*R*)-**3i** and (*S*)-**3i** were obtained in good yield and enantioselectivity (73% yield, 88% *ee*; 70% yield, 90% *ee*, see Scheme 2).

Furthermore, intermediates, which are present in the syntheses of several natural products were prepared.[2,3,15] Thus, (*R*)-**3j**, occurring in the total synthesis of the above mentioned aranorosin,[2] was prepared in 71% yield and 88% *ee*. The corresponding *S*-enantiomer (*S*)-**3j**, which was used for the total synthesis of 6′epi-aranorosin, was also obtained in 70% yield, but in lower optical purity (72% *ee*). Furthermore, (*R*)-**3k** (62% yield and 82% *ee*) and (*S*)-**3k** (67% yield and 84% *ee*), were prepared using this I/Li-exchange sequence.[15] Finally, we prepared the corresponding *S*-enantiomer of a precursor, which was used in the total synthesis of *ent*-stellettamide A.[3] Therefore, (*S*)-**3l** was obtained in 63% yield with 81% *ee*.




**Scheme 2.** Optically enriched α,β-unsaturated carbonyl derivatives of type **3** prepared by a stereoretentive I/Li sequence and subsequent cross-coupling with α,β-unsaturated carbonyl derivatives. [a] In this case the *ee*% of the starting secondary alkyl iodide was difficult to determine by chiral GC-analysis. It was estimated to be ca. 85% ±5% *ee*.

In summary, we have reported that γ-chiral Michael acceptors were readily prepared from chiral secondary alkyl iodides by an I/Li-exchange reaction and subsequent transmetalation to copper followed by addition to a broad range of 3-halogeno-α,β-unsaturated carbonyl derivatives. This method afforded γ-methyl unsaturated enones and enoates from relatively unfunctionalized secondary alkyllithiums. Only a few functional groups are tolerated by this method.[6b] Nevertheless, advanced precursors for the preparation of natural products were prepared to underline the synthetic value of this approach.

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## Conflict of interest

The authors declare no conflict of interest.

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