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# Stereoselective Functionalization of *β*-Iodo-α,*β*-Unsaturated Ketones via an Iodine–Copper Exchange Reaction

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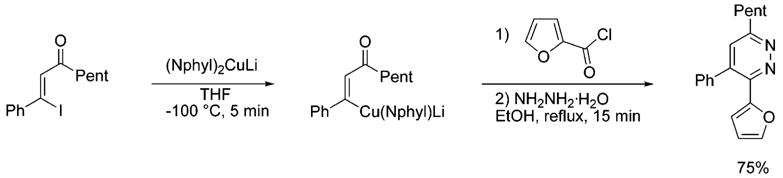
## ABSTRACT



***β*-Iodo-α,*β*-unsaturated carbonyl compounds undergo a stereoselective iodine–copper exchange reaction with $(Nphyl)_2CuLi$, providing the corresponding alkenyl cuprates with retention of the double bond configuration. No competitive addition/elimination was observed, and the resulting cuprates were successfully functionalized with various electrophiles.**

The preparation of functionalized organometallics is an important synthetic task since these reagents are key intermediates for the preparation of polyfunctional molecules.[1] In recent years, it was found that the iodine−magnesium exchange reaction is an excellent method for the preparation of various aryl, heteroaryl, and alkenyl Grignard reagents that bear ester, nitrile, amino, or nitro groups.[2] However, more sensitive functionalities, such as ketones, are usually not compatible with the presence of a C−Mg bond. To overcome these problems, we have developed an iodine−copper exchange reaction,[3] which allows a practical preparation of functionalized aryl and heteroaryl copper reagents in the presence of a keto group.[4] Herein, we wish to report a new application of this exchange reaction for performing a stereoselective metalation of α,*β*-unsaturated carbonyl compounds of type **1**.[5] The preparation of *β*-keto alkenylcopper

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(1) (a) Knochel, P., Ed. *Handbook of Functionalized Organometallics*; Wiley-VCH: Weinheim, Germany, 2005. (b) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376. (c) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104. (d) Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241. (e) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (f) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417.

(2) (a) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 897. (b) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017. (c) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (d) Staubitz, A.; Dohle, W.; Knochel, P. *Synthesis* **2003**, 233. (e) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319. (f) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080. (g) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215.

(3) For previous preparation of functionalized copper reagents, see: (a) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615. (b) Kondo, Y.; Matsudaira, T.; Sato, J.; Muraka, N.; Sakamoto, T. *Angew. Chem.* **1996**, *108*, 818; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736. (c) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5281. (d) Rieke, R. D.; Wehmeyer, R. H.; Wu, T. C.; Ebert, G. W. *Tetrahedron* **1989**, *45*, 443. (e) Ebert, G. W.; Cheasty, J. W.; Tehrani, S. S.; Aouad, E. *Organometallics* **1992**, *11*, 1560. (f) Ebert, G. W.; Pfennig, D. R.; Suchan, S. D.; Donovan, T. A. *Tetrahedron Lett.* **1993**, *34*, 2279. (g) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041. (h) Posner, G. H.; Whitten, C. E.; McFarland, P. *J. Am. Chem. Soc.* **1972**, *94*, 5106.

(4) (a) Piazza, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3263. (b) Yang, X.; Rotter, T.; Piazza, C.; Knochel, P. *Org. Lett.* **2003**, *5*, 1229. (c) Yang, X.; Knochel, P. *Synlett* **2004**, 81. (d) Yang, X.; Althammer, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 1665. (e) Yang, X.; Knochel, P. *Synlett* **2004**, 2303. (f) Calaza, M. I.; Yang, X.; Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 529.

(5) (a) Taniguchi, M.; Kobayashi, S.; Nakagawa, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4763. (b) Coperet, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422. (c) Zhang, Y.; O'Connor, B.; Negishi, E. *J. Org. Chem.* **1988**, *53*, 5588.

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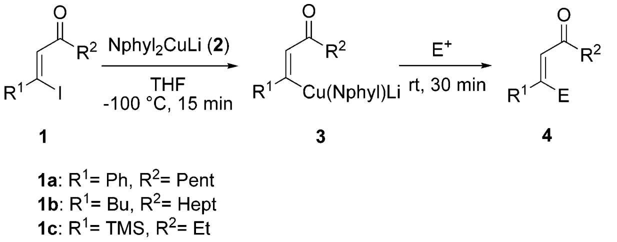
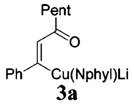
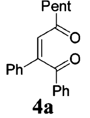
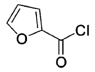
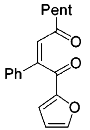
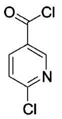
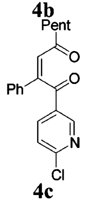
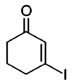
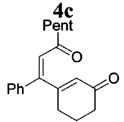
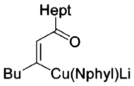
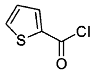
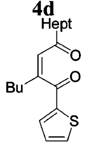
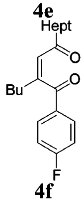
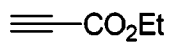
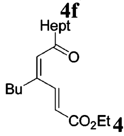
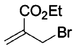
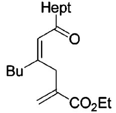
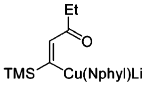
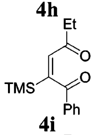
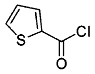
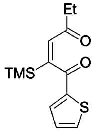
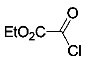
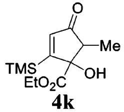
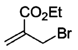
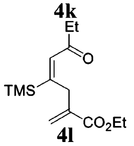
**Scheme 1.** Functionalization of $\beta$-Iodo-$\alpha$,$\beta$-Unsaturated Carbonyl Compounds via an Iodine−Copper Exchange



derivatives is a challenging task since $\beta$-substituted $\alpha$,$\beta$-unsaturated carbonyl compounds usually react with organometallics via an addition/elimination pathway.[6]

Thus, the $\beta$-iodo-$\alpha$,$\beta$-unsaturated ketones of type **1** reacted with $(Nphyl)_2CuLi$ (**2**) in THF at −100 °C for 15 min leading to the functionalized alkenylcoppers **3**, which were quenched with various electrophiles providing highly functionalized enones of type **4** in moderate to good yields (Scheme 1).[7] The reactions occurred stereoselectively with retention of the double bond configuration (>99%). The phenyl-substituted alkenyl cuprate **3a** reacted with various aromatic and heteroaromatic acid chlorides leading to diketones **4a**−**c** in moderate to good yields (78−83%, entries 1−3 of Table 1). The reaction of the cuprate **3a** with 3-iodo-2-cyclohexenone provided the addition−elimination product **4d** in 71% yield (entry 4). In a similar way, the bisalkyl-substituted alkenyl cuprate **3b** was readily acylated with 2-thiophenecarbonyl chloride and 4-fluorobenzoyl chloride, giving the diketones **4e**,**f** in 75−78% yields (entries 5 and 6). The carbocupration of ethyl propiolate with **3b** stereoselectively led to the dienone **4g** in 80% yield (entry 7). Furthermore, the allylation of cuprate **3b** proceeds smoothly with ethyl(2-bromomethyl)acrylate, providing the polyfunctional compound **4h** in 90% yield (entry 8). Even a change of the substituent $R^1$ in the $\beta$-iodo-$\alpha$,$\beta$-unsaturated ketones of type **1** from phenyl in **1a** or alkyl group in **1b** to the electron-donating trimethylsilyl group in **1c** did not affect the exchange reaction rate. The corresponding cuprate **3c** readily underwent acylation with benzoyl chloride and 2-thiophenecarbonyl chloride, providing the diketones **4i** and **4j** in 76−84% yields (entries 9 and 10). However, acylation with ethyl oxalyl chloride led after an

**Table 1.** Functionalization of $\beta$-Iodo-$\alpha$,$\beta$-Unsaturated Carbonyl Compounds via an Iodine−Copper Exchange

| entry | copper reagent | electrophile | product of type **4** | yield (%)[a] |
|---|---|---|---|---|
| 1 |  **3a** | PhCOCl |  **4a** | 83 |
| 2 | **3a** |  |  **4b** | 78 |
| 3 | **3a** |  |  **4c** | 81 |
| 4 | **3a** |  |  **4d** | 71 |
| 5 |  **3b** |  |  **4e** | 78 |
| 6 | **3b** | 4-FPhCOCl |  **4f** | 75 |
| 7 | **3b** |  |  **4g** | 80 |
| 8 | **3b** |  |  **4h** | 90 |
| 9 |  **3c** | PhCOCl |  **4i** | 84 |
| 10 | **3c** |  |  **4j** | 76 |
| 11 | **3c** |  |  **4k** | 72[b] |
| 12 | **3c** |  |  **4l** | 89 |

[a] Yield of analytically pure product. [b] Diastereomeric ratio = 8:1.

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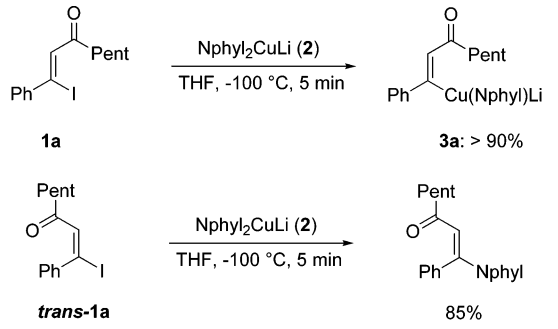
(6) (a) Krause, N., Ed. *Modern Organocopper Chemistry*; Wiley-VCH: Weinheim, Germany, 2002. (b) Taylor, R. J. K., Ed. *Organocopper Reagents*; IRL Press: Oxford, 1994.

(7) **Typical Procedure for the Synthesis of the Enone 4a.** A dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with CuCN (86 mg, 0.96 mmol) and dry THF (5 mL). A solution of neophyllithium (1.3 M $Et_2O$, 1.5 mL, 1.92 mmol) was added at −78 °C. The resulting reaction mixture was stirred at room temperature for 10 min, and then $Et_2O$ was removed carefully under vacuum. The remaining solution was cooled to −100 °C and cannulated into a solution of **1a** (262 mg, 0.8 mmol) in dry THF (2 mL). After 5 min, benzoyl chloride (280 mg, 2.0 mmol) was added and the mixture stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous $NH_4Cl$ solution (5 mL) and poured into water (10 mL). The aqueous phase was extracted with $Et_2O$ (3 × 10 mL), and the combined organic fractions were washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash chromatography, yielding **4a** (203 mg, 83%) as a colorless oil.

**Scheme 2.** Influence of the Double Bond Configuration of Enone **1** on the Reaction Outcome



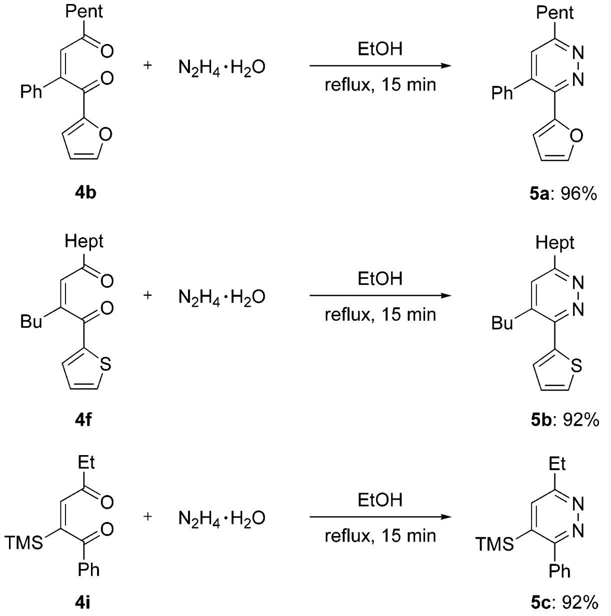
intramolecular aldol reaction to the five-membered enone **4k** in 72% yield in a 8:1 mixture of diastereoisomers (entry 11). Finally, the allylation of the cuprate **3c** with ethyl(2-bromomethyl)acrylate furnished ketone **4l** in 89% yield (entry 12).

The *cis*-configuration between the iodine and the carbonyl group in the $\beta$-iodo-unsaturated carbonyl derivatives of type **1** is crucial for the success of the exchange reaction, probably due to a chelation effect.[8] With the enone *trans*-**1a** under our standard reaction conditions, no iodine−copper exchange was observed in the reaction with $(Nphyl)_2CuLi$ (**2**). The only reaction observed here was an addition−elimination (Scheme 2).

The iodine−copper exchange reaction provides functionalized organocopper intermediates **3** and gives after acylation a simple access to diketones. These diketones are versatile building blocks for the synthesis of pyridazines. The treatment of the diketones **4b**, **4f**, and **4i** with $NH_2NH_2{\cdot}H_2O$ in refluxing EtOH for 15 min affords the pyridazines of type **5** in excellent yields (Scheme 3).[9]

In conclusion, we have shown that $\beta$-iodo-$\alpha$,$\beta$-unsaturated carbonyl compounds undergo a stereoselective iodine−copper exchange reaction under mild conditions and react with various electrophiles in good yields with retention of configuration. Further transformations of the products to pyridazines are described. Further extension of this method is currently underway in our laboratory.

**Scheme 3.** Synthesis of Pyridazines of Type **5**



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**Supporting Information Available:** Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

[9] Haddadin, M. J.; Agha, B. J.; Tabri, R. F. *J. Org. Chem.* **1979**, *44*, 494.