Preparation and Reactions of Functionalized Organocopper Reagents

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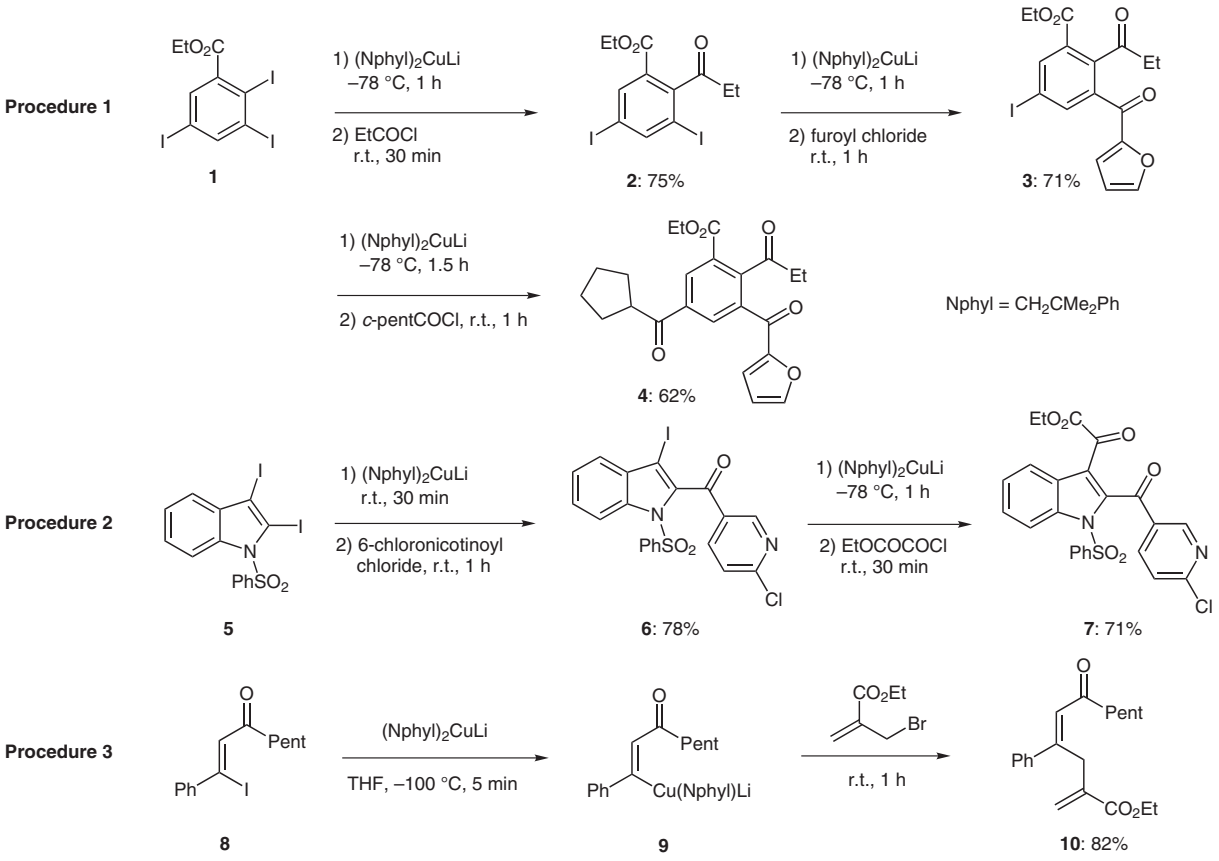
Received 4 March 2006; revised 13 April 2006

Abstract: Functionalized organocopper reagents have been prepared via an iodine–copper exchange by the reaction of aryl or alkenyl iodides with a sterically hindered cuprate reagent, lithium dineophylcuprate [$(Me_2PhCCH_2)_2CuLi$]. The resulting copper reagents react readily with various electrophiles leading to polyfunctionalized molecules. This method represents a unique protocol for the preparation of aryl-, heteroaryl- and alkenylcopper reagents.

Key words: functionalized organocopper reagents, iodine–copper exchange reaction, sterically hindered cuprate, polyfunctionalized molecules



Scheme 1

Introduction

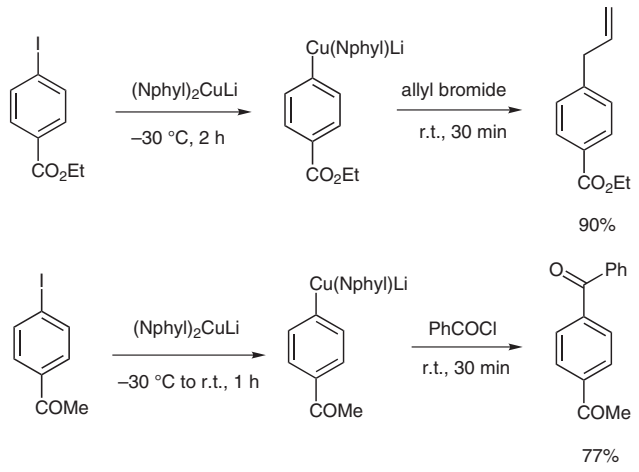
The preparation of functionalized organometallics is an important synthetic task, since these reagents allow the preparation of polyfunctional molecules.[1] Recently, we have found that the iodine–magnesium exchange reaction is an excellent method for the preparation of various functionalized aryl-, heteroaryl-, and alkenylmagnesium reagents.[2] The resulting Grignard reagents display high reactivity and good functional group tolerance. We have also developed an iodine–copper exchange reaction,[3] which allows for the practical preparation of functionalized aryl-, heteroaryl-, and alkenylcopper reagents in the presence of various functional groups, such as ketone, es-

SYNTHESIS 2006, No. 15, pp 2618–2623
Advanced online publication: 25.07.2006
DOI: 10.1055/s-2006-942496; Art ID: T03506SS

ter, nitrile, and halide (Scheme 1).[4] These unsaturated organocopper reagents combine good functional group tolerance and excellent reactivity with various electrophiles leading to polyfunctionalized products.[4]

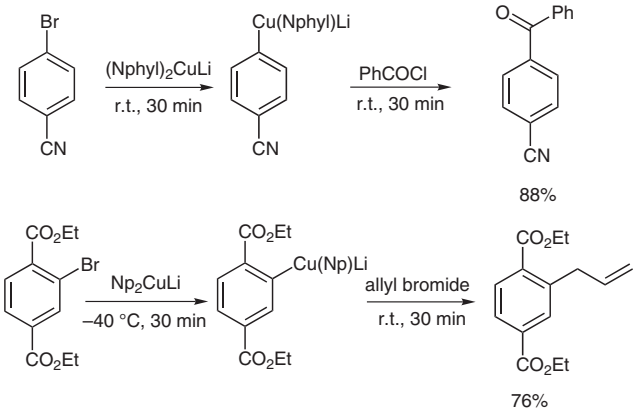
Scope and Limitations

The use of sterically hindered of lithium cuprates such as lithium dineopentylcuprate [$(Me_3CCH_2)_2CuLi$, abbreviated as Np_2CuLi] or lithium dineophylcuprate [$(Me_2PhCCH_2)_2CuLi$, abbreviated as $(Nphyl)_2CuLi$] are essential for the success of the reaction.[4a,5] Thus, ester or ketone groups are compatible with the generation of an arylcopper reagent via an iodine–copper exchange reaction. This exchange is completed at –30 °C within a few hours. Under these mild conditions, no attack on the ester or ketone occurs (Scheme 2).[4a]



Scheme 2 Functionalized arylcopper reagents obtained via an iodine–copper exchange reaction.

The rate of the halogen–copper exchange reaction greatly depends on the electron density of the aromatic or heteroaromatic ring. The more electron-poor the aromatic ring is, the faster the exchange reaction occurs.[6] Also, the presence of chelating groups *ortho* to the carbon–halogen bond strongly accelerates the exchange reaction and allows the bromine–copper exchange to take place under milder conditions than usual.[7] As expected, the iodine–copper exchange reaction is considerably faster than the corresponding bromine–copper exchange reaction (Scheme 3).

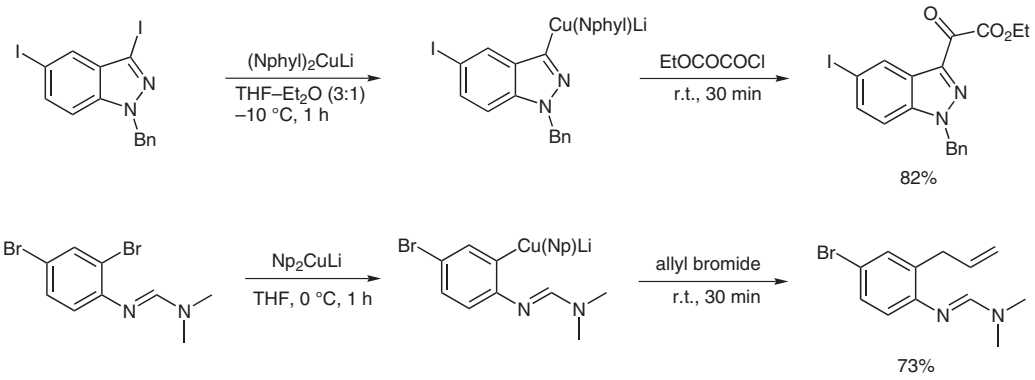


Scheme 3 Preparation of functionalized arylcopper reagents via a bromine–copper exchange reaction.

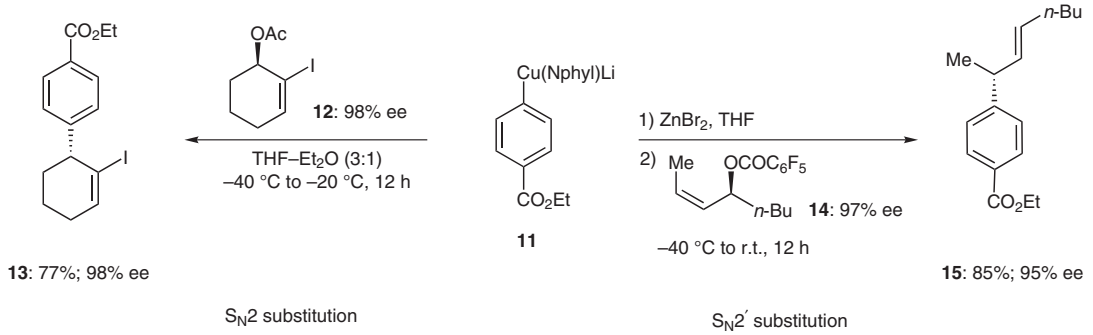
A selective mono-exchange reaction is observed with polyhalogenated aryl and heteroaryl compounds. After the first exchange, the electron density of the aromatic ring increases to such an extent that no further exchange reaction takes place (Scheme 4).[4e,6]

The mixed lithium neophyl(phenyl)cuprate **11** reacts with high S_N2 selectivity with chiral cyclic allylic acetates, such as **12** (98% ee), providing the chiral alkenyl iodide **13** (98% ee) in 77% yield. In the presence of zinc bromide, a dramatic change of regioselectivity is observed and the substitution reaction with the chiral acyclic pentafluorobenzoate **14** (97% ee) provides only the *anti*-S_N2' product **15** with 85% yield and 95% ee (Scheme 5).[8]

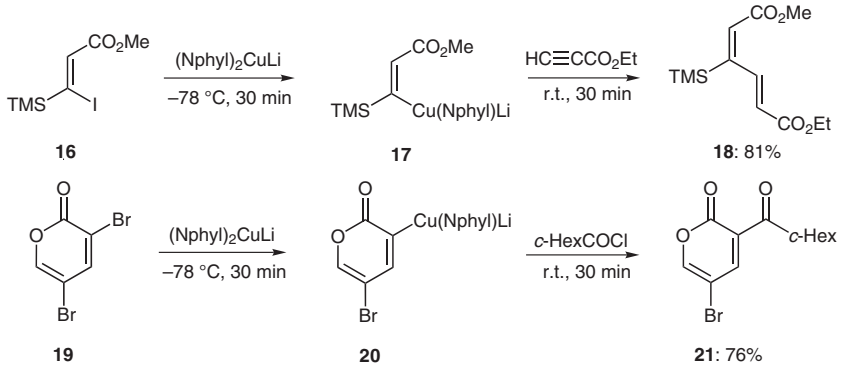
Interestingly, this method can also be extended to the preparation of highly functionalized alkenylcopper species (Scheme 6). Thus, the β-iodo unsaturated ester **16** can be readily converted into the copper species **17**. Carbocupration of ethyl propiolate with **17** stereoselectively leads to the diene **18** in 81% yield. The dibromide **19** undergoes a selective bromine–copper exchange reaction with lithium dineophylcuprate leading to the copper derivative **20**



Scheme 4 Selective halogen–copper exchange reaction for functionalization of dihalogenated aromatic compounds.



Scheme 5 Stereoselective substitutions of functionalized arylcopper reagents with chiral allylic electrophiles.



Scheme 6 Preparation of functionalized alkenylcopper reagents via a halogen–copper exchange reaction.

which can be readily acylated with cyclohexanecarbonyl chloride providing the ketone **21** in 76% yield.

In summary, the halogen–copper exchange reaction allows the preparation of highly functionalized organocopper reagents bearing various functional groups. Many of these copper reagents are versatile precursors for the preparation of complex molecules.

Procedures

Herein, we describe three typical procedures demonstrating the synthetic utility of functionalized organocopper reagents prepared by an iodine–copper exchange (Scheme 1). In Procedure 1, we report the successive iodine–copper exchange for the selective functionalization of polyhalogenated aromatics. Thus, the triiodobenzoate **1**[9] undergoes a selective mono-exchange reaction with lithium dineophylcuprate providing the copper derivative, which is readily acylated with propionyl chloride giving the ketone **2** in 75% yield. A second exchange can then be realized with lithium dineophylcuprate followed by acylation with 2-furoyl chloride to give the diketone **3** in 71% yield. Finally, a reaction with a further equivalent of lithium dineophylcuprate followed by acylation with cyclopentylcarbonyl chloride yields the triketone **4** in 62% yield. In the second procedure (Procedure 2), the selective functionalization of indoles in position 2 and 3 is achieved using an iodine–copper exchange reaction. Thus, the reaction of the 2,3-diiodoindole derivative **5**[10] with lithium dineophylcuprate followed by acylation with 6-chloronicotinoyl chloride provides the iodoindolyl ketone **6** in 78% yield. Treatment of **6** with a second equivalent of lithium dineophylcuprate followed by further acylation with ethyl oxaloyl chloride leads to the diketone **7** in 71% yield. In the last procedure (Procedure 3), the β-iodo-α,β-unsaturated ketone **8**[11] can be readily converted into the corresponding alkenylcopper compound **9** (–100 °C, 5 min). Its reaction with ethyl 2-(bromomethyl)acrylate furnishes the allylated compound **10** in 82% yield.

Unless otherwise indicated, all reactions were carried out with a magnetic stirring in flame-dried glassware under argon. Melting points were measured on a Büchi B 540 apparatus and were uncorrected. NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR (Varian XL 300). Chemical shifts were reported in ppm relative to TMS. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 1000. Low-resolution MS were recorded using a GC/MS combination of the type HP 6890 and MSD 5973 fitted with a HP-5 column (30 m × 0.25 mm × 0.25 μm). HRMS were recorded on a Finnigan-MAT 95Q spectrometer (EI, 70 eV). Flash column chromatographic purifications were carried out using Merck Kieselgel 60 (230–400 mesh ASTM). Commercially available starting materials with a purity >97% were used without further purification. Solvents were distilled and dried before use.

Neophyllithium[12]

A dry, argon-flushed, 500-mL round-bottom flask was charged with Li dust (3.0 g, 432 mmol) and 2-methyl-2-phenylethyl chloride

(14.0 mL, 86.9 mmol) in *n*-hexane (75 mL) and the mixture was refluxed overnight. The mixture was cooled to r.t., *n*-hexane was removed in vacuo and anhyd Et_2O was added. The resulting mixture was cannulated into a flame-dried Schlenk tube and centrifuged (2000 rpm, 30 min). The clear soln of neophyllithium thus obtained was titrated before use with menthol using *o*-phenanthroline as indicator[13] and can be stored at –30 °C for several days.

Ethyl 3,5-Diiodo-2-propionylbenzoate (2)

To a suspension of CuCN (614 mg, 6.8 mmol) in anhyd THF (20 mL) at –78 °C was added 1.5 M neophyllithium in Et_2O (9 mL, 13.6 mmol) and the resulting mixture was stirred at r.t. for 15 min. The resulting light yellow clear soln was cooled to –78 °C and a soln of ethyl 2,3,5-triiodobenzoate (3.0 g, 5.7 mmol) in anhyd THF (20 mL) was added via a cannula. The resulting mixture was stirred at this temperature for 1 h. Then anhyd NMP (1 mL) and propionyl chloride (15 mmol) were added successively. The resulting mixture was stirred at r.t. for 30 min. The mixture was quenched with sat. aq NH_4Cl (10 mL) and the resulting mixture was poured into H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic fractions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (*n*-pentane–Et_2O, 8:1) gave the desired product **2** as white solid; yield: 2.0 g (75%); mp 75 °C.

IR (KBr): 3410 (w), 2925 (s), 1721 (vs), 1560 (w), 1535 (s), 1461 (w), 1271 (vs), 1204 (m), 1103 (w), 1017 (w), 878 (w), 738 (vs), 704 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.37–8.36 (d, *J* = 1.7 Hz, 1 H), 8.34–8.33 (d, *J* = 1.7 Hz, 1 H), 4.38–4.31 (q, *J* = 7.1 Hz, 2 H), 2.89–2.82 (q, *J* = 7.1 Hz, 2 H), 1.39–1.36 (t, *J* = 7.1 Hz, 3 H), 1.31–1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.7, 163.7, 151.1, 148.5, 139.2, 130.3, 94.5, 92.8, 62.7, 36.6, 14.5, 7.8.

MS (EI, 70 eV): *m*/*z* (%) = 458 (5) [M^+], 429 (80), 401 (100), 373 (5), 356 (5), 274 (10), 201 (5), 74 (5).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{12}H_{12}I_2O_3$: 457.8876; found: 457.8851.

Ethyl 3-(2-Furoyl)-5-iodo-2-propionylbenzoate (3)

To a suspension of CuCN (360 mg, 4 mmol) in anhyd THF (15 mL) at –78 °C was added 1.5 M neophyllithium in Et_2O (5.4 mL, 8 mmol) and the resulting mixture was stirred at r.t. for 15 min. The resulting light yellow clear soln was cooled to –78 °C and a soln of ethyl 3,5-diiodo-2-propionylbenzoate (1.5 g, 3.3 mmol) in anhyd THF (10 mL) was added via a cannula. The resulting mixture was stirred at this temperature for 1 h. Then anhyd NMP (1 mL) and 2-furoyl chloride (8 mmol) were added successively. The resulting mixture was stirred at r.t. for 1 h. The mixture was quenched with sat. aq NH_4Cl (10 mL) and the resulting mixture was poured into H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic fractions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (*n*-pentane–Et_2O, 3:1) gave the desired product **3** as a white solid; yield: 1.0 g (71%); mp 117 °C.

IR (KBr): 3055 (w), 2926 (s), 1722 (vs), 1656 (s), 1565 (m), 1463 (s), 1264 (vs), 1178 (m), 1017 (w), 738 cm^{-1} (vs).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 1.7 Hz, 1 H), 8.21 (d, *J* = 1.7 Hz, 1 H), 7.73 (dd, *J* = 1.7 Hz, *J* = 0.8 Hz, 1 H), 7.19–7.18 (dd, *J* = 3.6 Hz, *J* = 0.8 Hz, 1 H), 6.64–6.62 (dd, *J* = 3.6 Hz, *J* = 1.7 Hz, 1 H), 4.42–4.36 (q, *J* = 7.1 Hz, 2 H), 2.91–2.84 (q, *J* = 7.1 Hz, 2 H), 1.42–1.37 (t, *J* = 7.1 Hz, 3 H), 1.24–1.19 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.4, 180.8, 164.4, 151.9, 148.7, 144.8, 141.8, 141.6, 138.2, 130.8, 122.6, 113.2, 93.2, 62.8, 38.3, 14.5, 8.1.

MS (EI, 70 eV): *m*/*z* (%) = 426 (2) [M^+], 397 (80), 381 (5), 301 (100), 229 (20), 174 (15), 95 (20), 75 (8).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{15}IO_5$: 425.9964; found: 425.9969.

Ethyl 5-(Cyclopentylcarbonyl)-3-(2-furoyl)-2-propionylbenzoate (4)

To a suspension of CuCN (373 mg, 4.1 mmol) in anhyd Et_2O (5 mL) at –78 °C was added 1.35 M neophyllithium in Et_2O (6.1 mL, 8.2 mmol) and the resulting mixture was stirred at r.t. for 15 min. The resulting light yellow clear soln was cooled to –78 °C and added via a cannula to a soln of the diketone **3** (1.0 g, 2.3 mmol) in anhyd THF (10 mL). The resulting mixture was stirred at this temperature for 1.5 h. Then, anhyd NMP (0.5 mL) and cyclopentanecarbonyl chloride (1.1 g, 8 mmol) were added successively. The resulting mixture was stirred at r.t. for 1 h. The mixture was quenched with sat. aq NH_4Cl (5 mL) and was poured into H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic fractions were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (*n*-pentane–Et_2O, 2:1) gave the desired product **4** as a yellow oil; yield: 0.57 g (62%).

IR (film): 3405 (w), 2942 (s), 1723 (vs), 1690 (vs), 1657 (vs), 1566 (s), 1463 (s), 1391 (m), 1299 (s), 1222 (s), 1018 (m), 950 (w), 795 (w), 769 (m), 593 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.63–8.62 (d, *J* = 1.7 Hz, 1 H), 8.42–8.41 (d, *J* = 1.7 Hz, 1 H), 7.64–7.63 (dd, *J* = 1.7 Hz, *J* = 0.8 Hz, 1 H), 7.11–7.10 (dd, *J* = 3.5 Hz, *J* = 0.8 Hz, 1 H), 6.55–6.54 (dd, *J* = 3.5 Hz, *J* = 1.7 Hz, 1 H), 4.35–4.31 (q, *J* = 7.1 Hz, 2 H), 3.68–3.63 (quint, *J* = 8.3 Hz, 1 H), 2.86–2.82 (q, *J* = 7.1 Hz, 2 H), 1.92–1.85 (m, 4 H), 1.68–1.60 (m, 4 H), 1.34–1.31 (t, *J* = 7.0 Hz, 3 H), 1.17–1.15 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.6, 199.8, 180.7, 164.1, 151.1, 147.8, 147.6, 136.2, 135.7, 132.1, 131.9, 128.9, 121.5, 112.2, 61.7, 46.0, 37.1, 29.1, 25.7, 13.4, 7.0.

MS (EI, 70 eV): *m*/*z* (%) = 396 (5) [M^+], 367 (70), 350 (10), 271 (100), 253 (10), 199 (35), 171 (15), 95 (20), 69 (15).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{23}H_{24}O_6$: 396.1573; found: 396.1588.

2-(6-Chloro-3-pyridinylcarbonyl)-3-iodo-1-(phenylsulfonyl)-1*H*-indole (6)

To a suspension of CuCN (540 mg, 6.0 mmol) in anhyd THF (10 mL) at –78 °C was added 1.5 M neophyllithium in Et_2O (8 mL, 12.0 mmol) and the resulting mixture was stirred at r.t. for 15 min. The resulting light yellow clear soln was cooled to –78 °C and a soln of the diiodoindole **5** (2.55 g, 5.0 mmol) in anhyd THF (15 mL) was added via a cannula. The resulting mixture was stirred at r.t. for 0.5 h and cooled to –78 °C. Then, anhyd NMP (1.5 mL) and a soln of 6-chloronicotinoyl chloride (2.6 g, 15 mmol) in anhyd THF (6 mL) were added successively. The resulting mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. aq NH_4Cl (10 mL) and the resulting mixture was poured into H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic fractions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (*n*-pentane–Et_2O, 5:1) gave the desired product **6** as a light yellow solid; yield: 2.04 g (78%); mp 62 °C.

IR (KBr): 3435 (vs), 2926 (w), 1673 (vs), 1581 (vs), 1447 (s), 1375 (s), 1364 (s), 1254 (m), 1176 (vs), 1089 (s), 1020 (w), 952 (m), 757 (m), 570 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.78–8.77 (d, *J* = 2.3 Hz, 1 H), 8.12–8.08 (dd, *J* = 8.4 Hz, *J* = 2.3 Hz, 1 H), 7.99–7.96 (d, *J* = 8.3 Hz, 1 H), 7.83–7.80 (m, 2 H), 7.52–7.29 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.9, 156.5, 151.8, 139.7, 136.8, 136.6, 136.1, 135.0, 132.2, 131.9, 129.7, 127.8, 125.7, 125.1, 123.7, 115.2, 75.0.

MS (EI, 70 eV): *m/z* (%) = 522 (20) [M$^+$], 380 (41), 254 (55), 226 (17), 191 (23), 164 (20), 141 (32), 114 (30), 77 (100).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{20}H_{12}ClIN_2O_3S$: 521.9302; found: 521.9277.

Ethyl [2-(6-Chloro-3-pyridinylcarbonyl)-1-(phenylsulfonyl)-1*H*-indol-3-yl](oxo)acetate (7)

To a suspension of CuCN (207 mg, 2.3 mmol) in anhyd THF (8 mL) at –78 °C was added 1.5 M neophyllithium in Et_2O (3.1 mL, 4.6 mmol) and the resulting mixture was stirred at r.t. for 15 min. The resulting light yellow clear soln was cooled to –78 °C and a soln of the iodoindole **6** (1.0 g, 1.92 mmol) in anhyd THF (6 mL) was added via a cannula. The resulting mixture was stirred at –78 °C for 1 h. Then, anhyd NMP (1 mL) and ethyl oxalyl chloride (685 mg, 5 mmol) in anhyd THF (6 mL) were added successively. The resulting mixture was stirred at r.t. for 1 h. The reaction was quenched with sat. aq NH_4Cl (10 mL) and the resulting mixture was poured into H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic fractions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (*n*-pentane–Et_2O, 2:1) gave **7** as white solid; yield: 0.7 g (71%); mp 53 °C.

IR (KBr): 3436 (vs), 1735 (s), 1677 (vs), 1582 (m), 1448 (w), 1380 (vs), 1365 (s), 1291 (m), 1152 (s), 1107 (s), 1040 (s), 952 (w) 753 (w), 684 (w), 569 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (d, *J* = 2.1 Hz, 1 H), 8.04–8.02 (dd, *J* = 8.35 Hz, *J* = 2.1 Hz, 1 H), 7.99–7.97 (d, *J* = 8.58 Hz, 1 H), 7.95–7.94 (d, *J* = 7.94 Hz, 1 H), 7.78–7.76 (d, *J* = 8.58 Hz, 2 H), 7.50–7.47 (t, *J* = 7.40 Hz, 1 H), 7.40–7.35 (m, 4 H), 7.32–7.30 (t, *J* = 7.15 Hz, 1 H), 4.12–4.08 (q, *J* = 6.91 Hz, 2 H), 1.18–1.15 (t, *J* = 6.91 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.6, 181.3, 163.0, 156.4, 151.1, 141.6, 139.1, 136.5, 135.6, 135.6, 132.8, 130.0, 128.0, 126.8, 126.6, 125.0, 123.1, 119.3, 114.8, 63.3, 14.2.

MS (EI, 70 eV): *m/z* (%) = 356 (8) [M – C_6H_3ClNO]$^+$, 283 (100), 170 (11), 140 (15), 112 (9), 76 (4).

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{24}H_{18}ClN_2O_6S$: 497.0574; found: 497.0528.

Ethyl (*E*)-2-Methylene-6-oxo-4-phenyl-4-undecenoate (10)

To a suspension of CuCN (323 mg, 3.6 mmol) in anhyd THF (10 mL) at –78 °C was added 1.5 M neophyllithium in Et_2O (4.8 mL, 7.2 mmol) and the resulting mixture was stirred at r.t. for 15 min. The resulting light yellow clear soln was recooled to –100 °C and was added via a cannula to a soln of the iodoenone **8** (1.0 g, 3.0 mmol) in anhyd THF (10 mL) at –100 °C. The resulting mixture was stirred at this temperature for 5 min. Ethyl (bromomethyl)acrylate (1.5 g, 8 mmol) was added successively and resulting mixture was stirred at r.t. for 1 h. The mixture was quenched with sat. aq NH_4Cl (8 mL) and was poured into H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic fractions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (*n*-pentane–Et_2O, 8:1) gave the desired product **10** as a colorless oil; yield: 0.77 g (82%).

IR (film): 3415 (w), 2957 (s), 2931 (s), 1714 (vs), 1686 (vs), 1601 (m), 1572 (m), 1446 (m), 1367 (m), 1247 (s), 1130 (s), 1075 (m), 951 (w), 761 (w), 697 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 2 H), 7.38–7.35 (m, 3 H), 6.67 (s, 1 H), 6.17–6.15 (dd, *J* = 2.65 Hz, *J* = 1.32 Hz, 1 H), 5.42–5.40 (dd, *J* = 3.00 Hz, *J* = 1.75 Hz, 1 H), 4.24–4.17 (q, *J* = 7.19 Hz, 2 H), 4.10–4.09 (t, *J* = 1.55 Hz, 2 H), 2.59–2.54 (t, *J* = 7.35 Hz, 2 H), 1.71–1.61 (m, 2 H), 1.38–1.28 (m, 4 H), 1.31–1.27 (t, *J* = 7.08 Hz, 3 H), 0.94–0.89 (t, *J* = 6.90 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 167.2, 153.5, 141.1, 138.1, 129.6, 129.0, 127.2, 126.6, 125.4, 61.2, 45.3, 33.0, 31.8, 24.3, 22.9, 14.5, 14.3.

MS (EI, 70 eV): *m/z* (%) = 314 (13) [M$^+$], 285 (10), 241 (100), 215 (30), 187 (18), 169 (11), 141 (13), 115 (10), 91 (4), 102 (2).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{20}H_{26}O_3$: 314.1882; found: 314.1904.

Acknowledgment

We thank the Fonds der Chemischen Industrie and the Ludwig-Maximilians-University (Munich) for the financial support. We thank the BASF AG (Ludwigshafen), Degussa (Hanau) and Chemetall GmbH (Frankfurt) for the generous gift of chemicals.

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