Successive Iodine-Magnesium or -Copper Exchange Reactions for the Selective Functionalization of Polyhalogenated Aromatics

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Supporting Information

General considerations

Unless otherwise indicated, all reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame-dried glassware under argon. Syringes used to transfer reagents and solvent were purged with argon prior to use. Reactions were monitored by gas chromatography (GC and GC-MS) or thin layer chromatography (TLC).

Organolithium solutions were titrated using the method of Paquette.¹

Preparation of lithium dineopentylcuprate (Np₂CuLi):²

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of neopentyl iodide (0.3 mL, 2.2 mmol) in diethyl ether (2 mL). The solution was cooled to -78 °C and *t*-BuLi (1.5 M/*n*-pentane, 3.1 mL, 4.6 mmol) was added dropwise. The resulting mixture was stirred for 45 min at -78 °C and then warmed to rt. After stirring for another 45 min the mixture was then cannulated into a suspension of CuCN (110 mg, 1.2 mmol) in THF (1 mL) precooled to -78 °C. The reaction mixture was allowed to warm to 0 °C for 15 min to furnish the expected dialkylcuprate ready to use.

Preparation of lithium dineophylcuprate (Nphyl₂CuLi):³

A dry and argon flushed 500 mL round-bottom flask was charged with lithium dust (3.0 g, 432 mmol) and 2,2-dimethyl-2-phenylethyl chloride (14.0 mL, 86.9 mmol) in *n*-hexane (75 mL). The reaction mixture was refluxed overnight. After cooling to rt the *n*-hexane was removed *in vacuo* and then dry diethyl ether was added. The resulting mixture was cannulated into a flame dried Schlenk tube and centrifuged (2000 rpm, 30 min). The clear solution of neophyllithium thus obtained was titrated before use with menthol using *o*-phenanthroline as indicator and could be stored at -30 °C for several days.

A dry and argon flushed 25 mL flask was charged with CuCN (110 mg, 1.2 mmol). Dry diethyl ether (1 mL) was added and the resulting suspension was cooled to 0 °C. The freshly titrated solution of neophyllithium was then added slowly and the mixture was quickly warmed to rt and stirred for 10 min, until a clear yellow solution of the desired cuprate was obtained.

Ethyl 2,3,5-triiodobenzoate (1):

A 500 mL round-bottomed flask was charged with a solution of 2,3,5-triiodobenzoic acid⁴ (10 g, 20 mmol) in ethanol (60 mL). Conc. H₂SO₄ (3 mL) was added slowly and the resulting

¹ Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.

² Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

³ (a) Cano, A.; Cuenca, T.; Galakov, M.; Rodríguez, G. M.; Royo, P.; Cardin, C. J.; Convery, M. A. *J. Organomet. Chem.* **1995**, *493*, 17. (b) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

solution was refluxed overnight. After cooling to rt, the reaction solution was extracted with CH_2Cl_2 (3×150 ml). The organic fractions were washed with 10% aqueous NaHCO_3 solution (3×100 ml), brine (150 ml), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 20:1) yielded 9.95 g (95% yield) of **1** as a white solid, mp 91 °C. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ = 8.23 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ = 166.5, 149.0, 142.2, 137.2, 113.7, 106.9, 94.1, 62.9, 14.5. IR (film, cm^{-1}): 3440 (w), 2978 (w), 1736 (vs), 1270 (vs), 1184 (vs), 773 (w). MS (EI, 70 ev): 528 (100) [M^+], 500 (23), 483 (54), 455 (18), 373 (10), 328 (10), 218 (10), 201 (32), 74 (20). HRMS (EI): calcd. for $\text{C}_9\text{H}_7\text{I}_3\text{O}_2$ [M^+]: 527.7580, found: 527.7579.

4,6-Diiodo-3-phenyl-2-benzofuran-1(3H)-one (**4a**):

Typical procedure A: A dry and argon flushed 50 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of ethyl 2,3,5-triiodobenzoate (528 mg, 1.0 mmol) in dry diethyl ether (30 mL). *i*-PrMgCl (1.0 M/diethyl ether, 1.1 mmol, 1.1 equiv.) was added slowly at -90°C and the resulting mixture was warmed up slowly to -78°C and stirred at this temperature for 2 h to complete the iodine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Then benzaldehyde (318 mg, 3.0 mmol, 3.0 equiv.) was added. The mixture was warmed up to 0°C and was quenched after 1 h with saturated aqueous NH_4Cl solution and poured into water (20 ml). The aqueous phase was extracted with diethyl ether (3×50 mL). The organic fractions were washed with brine (30 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 10:1) yielded 356 mg (77% yield) of **4a** as a white solid, mp 180°C . $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ = 8.36 (d, J = 1.3 Hz, 1H), 8.29 (d, J = 1.3 Hz, 1H), 7.46-7.32 (m, 3H), 7.24-7.15 (m, 2H), 6.14 (s, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ = 167.5, 151.3, 151.3, 134.3, 133.2, 129.9, 129.8, 129.2, 128.9, 95.2, 91.2, 85.4. IR (film, cm^{-1}): 3070 (w), 3060 (w), 1763 (vs), 1562 (w), 1436 (s), 1277 (s), 1231 (s), 1151 (s), 1064 (vs), 971 (vs), 881 (m). MS (EI, 70 ev): 462 (100) [M^+], 385 (11), 357 (19), 163 (49), 105 (87). HRMS (EI): calcd. for $\text{C}_{14}\text{H}_8\text{I}_2\text{O}_2$ [M^+]: 461.8614, found: 461.8576.

4,6-Diiodo-3-thiophen-2-yl-3H-isobenzofuran-1-one (**4b**):

The reaction was carried out according to typical procedure A with ethyl 2,3,5-triiodobenzoate (264 mg, 0.5 mmol), *i*-PrMgCl (1.0 M/diethyl ether, 0.6 mmol, 1.2 equiv.) and 2-thiophenecarboxaldehyde (168 mg, 1.5 mmol, 3.0 equiv.). Standard workup and purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 15:1) yielded 195 mg (83% yield) of **4b** as a white solid, mp 160°C . $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ = 8.39 (d, J = 1.3 Hz, 1H), 8.27 (d, J = 1.3 Hz, 1H), 7.42 (dd, J = 5.3 Hz, J = 0.9 Hz, 1H), 7.18 (dd, J = 3.5 Hz, J = 0.9 Hz, 1H), 7.04 (dd, J = 5.3 Hz, J = 3.5 Hz, 1H), 6.41 (s, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ = 166.9, 151.5, 150.7, 135.9, 134.4, 130.4, 129.5, 128.4, 127.2, 95.6, 91.3, 79.9. IR (film, cm^{-1}): 3057 (w), 1759 (vs), 1561 (m), 1439 (s), 1385 (s), 1278 (s), 1232 (s), 1149 (m), 1067 (s), 953 (s), 726 (vs). MS (EI, 70 ev): 468 (100) [M^+], 424 (16), 356 (10), 297 (52), 170 (49). HRMS (EI): calcd. for $\text{C}_{12}\text{H}_6\text{I}_2\text{O}_2\text{S}$ [M^+]: 467.8178, found: 467.8154.

Ethyl 2-[(diallylamino)methyl]-3,5-diiodobenzoate (**4c**):

The reaction was carried out according to typical procedure A with ethyl 2,3,5-triiodobenzoate (264 mg, 0.5 mmol), *i*-PrMgCl (1.0 M/diethyl ether, 0.6 mmol, 1.2 equiv.) and diallyl(methylene)ammonium trifluoroacetate (3 mmol, 6.0 equiv.). Standard workup and purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 15:1) yielded 217 mg (85% yield) of **4c** as a yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ = 8.20 (d, J = 1.8 Hz, 1H),

⁴ 2,3,5-Triiodobenzoic acid is commercially available from Aldrich.

7.72 (d, $J = 1.8$ Hz, 1H), 5.83-5.67 (m, 2H), 5.16-5.05 (m 4H) 4.31 (q, $J = 7.1$ Hz, 2H), 3.86 (s, 2H), 3.01 (d, $J = 6.6$ Hz, 4H), 1.36 (t, $J = 7.1$ Hz, 3H). ^{13}C -NMR (CDCl_3 , 75 MHz): $\delta = 167.0, 148.3, 148.0, 137.1, 136.9, 134.7, 117.8, 102.4, 92.4, 61.3, 59.9, 55.6, 14.2$. IR: (film, cm^{-1}): 3074 (w), 2978 (w), 1727 (vs), 1539 (w), 1432 (w), 1265 (vs), 1199 (s), 919 (m). MS (EI, 70 eV): 470 (100), 424 (35), 387 (17). HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{19}\text{I}_2\text{N O}_2$ [M^+]: 510.9505, found: 510.9515.

Ethyl 2-cyano-3,5-diiodobenzoate (4d):

The reaction was carried out according to typical procedure A with ethyl 2,3,5-triiodobenzoate (5.28 g, 10 mmol), *i*-PrMgCl (1.0 M/ diethyl ether, 11.0 mmol, 1.1 equiv.) and acetyl bromide (3.69 g, 30.0 mmol, 3.0 equiv.). Standard workup and purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 10:1) yielded 3.84 g (90% yield) of **4d** as a white solid, mp 113 °C. ^1H -NMR (CDCl_3 , 300 Hz): $\delta = 8.52$ (d, $J = 1.5$ Hz, 1H), 8.40 (d, $J = 1.5$ Hz, 1H), 4.47 (q, $J = 7.1$ Hz, 2H), 1.46 (t, $J = 7.1$ Hz, 3H). ^{13}C -NMR (CDCl_3 , 75 Hz): $\delta = 162.3, 151.2, 139.7, 136.2, 120.0, 117.9, 103.0, 100.1, 63.5, 14.4$. IR (film, cm^{-1}): 3426 (s), 2900 (w), 2228 (w), 1723 (vs), 1555 (s), 1475(w), 1422 (w), 1368 (m), 1272(vs), 1256(vs), 1193 (m), 1175(w), 1071 (m), 879 (m), 781 (m), 620(m). MS (EI, 70 eV): 427 (95) [M^+], 412 (5), 399 (88), 382 (100), 355 (60), 272 (10), 227 (40), 201 (10), 127 (15), 100 (100), 74 (20). HRMS (EI): calcd. for $\text{C}_{10}\text{H}_7\text{I}_2\text{N O}_2$ [M^+]: 426.8566, found: 426.8553.

Ethyl 2-acetyl-3,5-diiodobenzoate (4e):

Typical procedure B: A dry and argon flushed 50 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of ethyl 2,3,5-triiodobenzoate (528 mg, 1.0 mmol) in dry diethyl ether (30 mL). $(\text{Np})_2\text{CuLi}$ (1.1 mmol, 1.1 equiv.) was added slowly at -78°C and the resulting mixture was stirred at this temperature for 20 min to complete the iodine-copper exchange (checked by GC-MS analysis of reaction aliquots). Then acetyl bromide (369 mg, 3.0 mmol, 3.0 equiv.) was added. The mixture was warmed up to 0°C and was quenched after 30 min with saturated aqueous NH_4Cl solution and poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3×80 mL). The organic fractions were washed with brine (80 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 10:1) yielded 310 mg (70% yield) of **4e** as a white solid, mp 76°C . ^1H -NMR (CDCl_3 , 300 Hz): $\delta = 8.29$ (s, 1H), 8.25 (s, 1H), 4.28 (q, $J = 7.1$, 2H), 2.51 (s, 3H), 1.30 (t, $J = 7.1$, 3H). ^{13}C -NMR (CDCl_3 , 75 Hz): $\delta = 202.5, 162.3, 149.8, 147.1, 137.8, 128.7, 93.2, 90.7, 61.4, 29.5, 13.0$. IR (film, cm^{-1}): 3409 (w), 2982 (w), 1712 (vs), 1711 (vs), 1557 (s), 1533(s), 1470 (w), 1422(m), 1353 (s), 1238(vs), 1205(vs), 1113 (m), 1021(s), 885 (m), 755 (m), 567(m). MS (EI, 70 eV): 444 (30) [M^+], 429 (80), 401 (100), 373 (15), 357 (10), 229 (10), 201 (12), 74 (15). HRMS (EI): calcd. for $\text{C}_{11}\text{H}_{10}\text{I}_2\text{O}_3$ [M^+]: 443.8719, found: 443.8742.

Ethyl 2-allyl-3,5-diiodobenzoate (4f):

The reaction was carried out according to typical procedure B with ethyl 2,3,5-triiodobenzoate (528 mg, 1.0 mmol), $(\text{Np})_2\text{CuLi}$ (1.1 mmol, 1.1 equiv.) and allyl bromide (362 mg, 3.0 mmol, 3.0 equiv.). Standard workup and purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 20:1) yielded 274 mg (62%) of **4f** as a white solid, mp 68°C . ^1H -NMR (CDCl_3 , 300 MHz): $\delta = 8.32$ (s, 1H), 8.04 (s, 1H), 5.95-5.80 (m, 1H), 5.08 (d, $J = 11$ Hz, 1H), 4.98 (d, $J = 17$ Hz, 1H), 4.34 (q, $J = 7.2$ Hz, 2H), 3.84 (d, $J = 5.5$ Hz, 2H), 1.37 (t, $J = 7.2$ Hz, 3H). ^{13}C -NMR (CDCl_3 , 75 MHz): $\delta = 165.7, 150.2, 141.9, 138.8, 134.6, 133.8, 116.5, 104.4, 91.4, 61.7, 41.6, 14.2$. IR: (film, cm^{-1}): 2981 (w), 1722 (vs), 1635 (w), 1431 (m), 1250 (vs), 1183 (m), 1094 (m), 1024 (m), 878 (w), 781 (m), 706 (w). MS (EI, 70 eV): 442 (100) [M^+], 427 (60), 399 (58), 241 (30) 115 (76). HRMS (EI): calcd. for $\text{C}_{12}\text{H}_{12}\text{I}_2\text{O}_2\text{S}$ [M^+]: 441.8927, found: 441.8913.

Ethyl 3-allyl-2-[(diallylamino)methyl]-5-iodobenzoate (6a):

A dry and argon flushed 250 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of ethyl 2-[(diallylamino)methyl]-3,5-diiodobenzoate (1.47 g, 2.9 mmol) in diethyl ether (150 mL). (Np)₂CuLi (5.8 mmol, 2.0 equiv.) was added slowly at –78°C and the resulting mixture was stirred at this temperature for 2 h to complete the iodine-copper exchange (checked by GC-MS analysis of reaction aliquots). Then allyl bromide (1.05 g, 8.7 mmol, 3.0 equiv.) was added. The mixture was warmed up to rt and was quenched after 1.5 h with saturated aqueous Na₂CO₃ solution (20 ml) and poured into water (100 ml). The aqueous phase was extracted with CH₂Cl₂ (3 × 120 mL). The organic fractions were washed with brine (80 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, *n*-pentane/diethyl ether = 50:1) yielded 804 mg (65% yield) of **6a** as a yellow oil. ¹H-NMR (CDCl₃, 300 MHz): δ = 7.68 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 5.96-5.68 (m, 3H), 5.14-4.92 (m, 6H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 3.44 (d, *J* = 6.2 Hz, 4H), 2.98 (d, *J* = 6.2 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz): δ = 168.1, 141.9, 140.3, 136.9, 136.3, 136.1, 135.3, 135.2, 117.5, 116.6, 91.8, 61.1, 55.9, 50.9, 36.9, 14.2. IR (film, cm⁻¹): 3077 (w), 2978 (m), 1725 (vs), 1570 (m), 1446 (m), 1271 (vs), 1150 (vs), 919 (vs). MS (EI, 70 ev): 425 (2) [M⁺], 396 (10), 384 (100), 338 (30), 281 (13), 172 (18) 128 (37). HRMS (EI): calcd. for C₁₉ H₂₄ I N O₂ [M⁺]: 425.0852, found: 425.0843.

2-Cyano-5-iodo-isophthalic acid diethyl ester (6b):

Typical Procedure C: A dry and argon flushed 100 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of ethyl 2-cyano-3,5-diiodobenzoate (427 mg, 1.0 mmol) in dry diethyl ether (50 mL). (Nphyl)₂CuLi (1.5 M/diethyl ether, 1.1 mmol, 1.1 equiv.) was added slowly at –78°C. After 1 h the iodine-copper exchange was completed (checked by GC-MS analysis of reaction aliquots). Then ethyl chloroformate (297 mg, 3.0 mmol, 3 equiv.) was added. The mixture was warmed up to 0°C and was quenched after 3 h with saturated aqueous NH₄Cl solution and poured into water (25 ml). The aqueous phase was extracted with diethyl ether (3 × 80 mL). The organic fractions were washed with brine (80 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, *n*-pentane/diethyl ether = 10:1) yielded 261 mg (70% yield) of **6b** as a colourless needle crystalline, mp 105 °C. ¹H-NMR (CDCl₃, 300 MHz): δ = 8.45 (s, 2H), 4.42 (q, *J* = 7.1, 4H), 1.38 (t, *J* = 7.1, 6H). ¹³C-NMR (CDCl₃, 75 MHz): δ = 163.2, 143.1 136.6 114.8, 111.7, 99.0, 63.4, 14.4. IR (film, cm⁻¹): 3441 (w), 2984 (w), 2238 (w), 1737 (vs), 1565 (m), 1470 (w), 1446 (w), 1394 (w), 1286 (vs), 1245 (vs), 1208 (vs), 1022 (s), 792 (m). MS (EI, 70 ev): 373 (48) [M⁺], 345 (17), 328 (73), 316 (21), 300 (100), 273 (62), 255 (8), 229 (22), 100 (37). HRMS (EI): calcd. For C₁₃ H₁₂ I N O₄ [M⁺]: 372.9811, found: 372.9825.

Ethyl 2-acetyl-3-allyl-5-iodobenzoate (6c):

The reaction was carried out according to typical procedure C with ethyl 2-acetyl-3,5-diiodobenzoate (222 mg, 0.5 mmol), (Nphyl)₂CuLi (1.5 M/ diethyl ether, 0.6 mmol, 1.2 equiv.) and allyl bromide (181 mg, 1.5 mmol, 3.0 equiv.). Standard workup and purification by flash chromatography (SiO₂, *n*-pentane/diethyl ether = 20:1) yielded 135 mg (75% yield) of **6c** as a yellow oil. ¹H-NMR (CDCl₃, 300 MHz): δ = 8.19 (d, *J* = 1.8 Hz, 1H), 7.74 (d, *J* = 1.8 Hz, 1H), 5.92-5.77 (m, 1H), 5.11 (ddt, *J* = 10 Hz, *J* = 1.3, *J* = 1.3, 1H), 5.03 (ddt, *J* = 17 Hz, *J* = 1.3, *J* = 1.6, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.24 (d, *J* = 6.2 Hz, 2H), 2.46 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz): δ = 204.6, 164.4, 143.3, 142.9, 137.6, 136.9, 135.3, 128.4, 117.6, 93.7, 61.9, 36.0, 32.2, 14.0. IR (film, cm⁻¹): 3079 (vw), 2981 (w), 1720 (vs), 1570 (s), 1446 (m), 1281 (vs), 1175 (s), 919 (m), 791 (m). MS (EI, 70 ev): 358 (8) [M⁺], 343 (51), 315 (38), 297 (100), 185 (25). HRMS (EI): calcd. for C₁₄ H₁₅ I O₃ [M⁺]: 358.0066, found: 358.0104.

Ethyl 2-acetyl-3-[2-(ethoxycarbonyl)-2-propenyl]-5-iodo benzoate (6d):

The reaction was carried out according to typical procedure C with ethyl 2-acetyl-3,5-diiodobenzoate (222 mg, 0.5 mmol), (Nphyl)₂CuLi (1.5 M/ diethyl ether, 0.6 mmol, 1.1 equiv.) and ethyl 2-bromomethyl-acrylate (290 mg, 1.5 mmol, 3 equiv.). Standard workup and purification by flash chromatography (SiO₂, *n*-pentane/diethyl ether = 5:1) yielded 149 mg (70%) of **6d** as a white solid, mp 73 °C. ¹H-NMR (CDCl₃, 300 MHz): δ = 8.22 (d, *J* = 1.8 Hz, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 6.33 (m, 1H), 5.46-5.42 (m, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.51 (s, 2H), 2.50 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz): δ = 204.7, 166.1, 164.4, 143.6, 142.8, 138.2, 137.3, 136.7, 128.6, 128.1, 93.7, 62.0, 61.0, 34.1, 32.2, 14.1, 14.0. IR (film, cm⁻¹): 2976 (w), 1724 (vs), 1712 (vs), 1570 (w), 1281 (vs), 1166 (s), 1155 (s), 788 (w). MS (EI, 70 ev): 430 (1) [M⁺], 415 (77), 385 (12), 369 (85), 341 (100); 313 (18), 297 (38). HRMS (EI): calcd. for C₁₇ H₁₉ I O₅ [M⁺]: 430.0277, found: 430.0275.

Ethyl 2-acetyl-5-iodo-3-propionylbenzoate (6e):

The reaction was carried out according to typical procedure C with ethyl 2-acetyl-3,5-diiodobenzoate (3.0 g, 6.7 mmol), (Nphyl)₂CuLi (1.5 M/ diethyl ether, 7.4 mmol, 1.1 equiv.) and propionyl chloride (1.9 g, 20.1 mmol, 3 equiv.). Standard workup and purification by flash chromatography (SiO₂, *n*-pentane/diethyl ether = 10:1) yielded 1.6 g (66% yield) of **6e** as a yellow solid, mp 85 °C. ¹H-NMR (CDCl₃, 300 MHz): δ = 8.46 (d, *J* = 1.8 Hz, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.93 (q, *J* = 7.1 Hz, 2H), 2.59 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz): δ = 203.9, 199.8, 163.9, 144.3, 142.4, 141.1, 137.7, 130.2, 93.2, 62.3, 33.2, 31.4, 14.0, 7.8. IR (film, cm⁻¹): 3080 (vw), 2974 (m), 1720 (vs), 1703 (vs), 1570 (m), 1347 (m), 1286 (vs), 1242 (vs), 1189 (vs), 1017 (m), 792 (m). MS (EI, 70 ev): 374 (1) [M⁺], 359 (24), 345 (100), 331 (32), 313 (18), 299 (84). HRMS (EI): calcd. for C₁₄ H₁₅ I O₄ [M⁺]: 374.0015, found: 373.9999.

Ethyl 2-acetyl-3-(cyclopropylcarbonyl)-5-iodobenzoate (6f):

The reaction was carried out according to typical procedure C with ethyl 2-acetyl-3,5-diiodobenzoate (222 mg, 0.5 mmol), (Nphyl)₂CuLi (1.5 M/diethyl ether, 0.6 mmol, 1.2 equiv.) and cyclopropane-carbonyl chloride (157 mg, 1.5 mmol, 3.0 equiv.). Standard workup and purification by flash chromatography (SiO₂, *n*-pentane/diethyl ether = 10:1) yielded 124 mg (64% yield) of **6f** as a white solid, mp 100°C. ¹H-NMR (CDCl₃, 300 MHz): δ = 8.45 (d, *J* = 1.8 Hz, 1H), 8.39 (d, *J* = 1.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 2.50-2.40 (m, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.30-1.21 (m, 2H), 1.17-1.07 (m, 2H). ¹³C-NMR (CDCl₃, 75 MHz): δ = 203.7, 199.9, 163.9, 143.8, 141.9, 141.1, 139.1, 130.1, 93.2, 62.3, 31.7, 19.3, 14.0, 12.9, 9.1. IR (film, cm⁻¹): 3080 (w), 2999 (m), 1727 (vs), 1697 (vs), 1673 (vs), 1568 (vs), 1554 (s), 1378 (vs), 1284 (vs), 1241 (vs), 1183 (vs), 1008 (vs), 794 (s). MS (EI, 70 ev): 371 (100), 343 (11), 325 (34), 301 (40). HRMS (EI): calcd. for C₁₅ H₁₅ I O₄ [M⁺]: 386.0015, found: 386.0029.

Ethyl 2-acetyl-3-benzoyl-5-iodobenzoate (6g):

The reaction was carried out according to typical procedure C with ethyl 2-acetyl-3,5-diiodobenzoate (444 mg, 1.0 mmol), (Nphyl)₂CuLi (1.5 M/ diethyl ether, 1.1 mmol, 1.1 equiv.) and benzoyl chloride (422 mg, 3.0 mmol, 3.0 equiv.). Standard workup and purification by flash chromatography (SiO₂, *n*-pentane/diethyl ether = 10:1) yielded 295 mg (70% yield) of **6g** as a colorless oil. ¹H-NMR (CDCl₃, 300 Hz): δ = 8.40 (d, *J* = 1.8 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.70-7.67 (m, 2H), 7.59-7.54 (m, 1H), 7.45-7.40 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 1.33 (t, *J* = 7.1, 3H). ¹³C-NMR (CDCl₃, 75 Hz): δ = 203.7, 195.0, 164.4, 141.9, 141.8, 141.5, 139.5, 136.5, 134.3, 130.7, 130.5, 129.1, 93.2, 62.8, 32.6, 14.4. IR (film, cm⁻¹): 3064 (w), 2981 (w), 2935 (w), 1716 (vs), 1714 (vs), 1667 (vs), 1596 (s), 1566(s),

1449 (m), 1366(w), 1352 (m), 1283(vs), 1248(vs), 1213 (m), 1179(s), 1115 (m), 1055 (m), 976 (s), 895 (m), 775 (m), 710 (s), 689 (m), 582(m). MS (EI, 70 ev): 422 (10) [M^+], 407 (100), 379 (45), 301 (70), 229 (20), 174 (10), 151 (10), 105 (50), 77 (45). HRMS (EI): calcd. for $C_{18}H_{15}IO_4$ [M^+]: 422.0015, found: 422.0006.

Ethyl 2-acetyl-3-furoyl-5-iodobenzoate (6h):

The reaction was carried out according to typical procedure C with ethyl 2-acetyl-3,5-diiodobenzoate (444 mg, 1.0 mmol), $(N\text{phyl})_2\text{CuLi}$ (1.5 M/ diethyl ether, 1.1 mmol, 1.1 equiv.) and furoyl chloride (422 mg, 3.0 mmol, 3.0 equiv.). Standard workup and purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 10:1) yielded 280 mg (68% yield) of **6g** as a light yellow solid, mp 128 °C. $^1\text{H-NMR}$ (CDCl_3 , 300 Hz): δ = 8.40 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 7.65-7.64 (dd, J = 1.7 Hz, J = 0.8 Hz, 1H), 7.12-7.11 (dd, J = 3.5 Hz, J = 0.8 Hz, 1H), 6.55-6.54 (dd, J = 3.5 Hz, J = 1.7 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.52 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 Hz): δ = 203.6, 180.8, 164.3, 151.9, 148.7, 144.9, 141.8, 141.7, 138.2, 130.5, 122.6, 113.2, 93.3, 62.8, 32.7, 14.4. IR (film, cm^{-1}): 3421 (m), 3076 (w), 2983 (w), 1718 (vs), 1697 (vs), 1649 (vs), 1562 (s), 1463(s), 1385(m), 1284(vs), 1253 (vs), 1178(s), 1149 (m), 1018 (s), 983 (w), 866 (m), 779 (m), 708 (w), 580(w). MS (EI, 70 ev): 412 (20) [M^+], 397 (30), 384 (25), 301 (100), 229 (20), 174 (10), 95 (20), 75 (10). HRMS (EI): calcd. for $C_{16}H_{13}IO_5$ [M^+]: 411.9808, found: 411.9834.

Ethyl 2-acetyl-3-cyclopropanoylcarbonyl-5-propionyl-benzoate (8a):

Typical procedure D: A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of ethyl 2-acetyl-3-cyclopropanoyl-5-iodobenzoate (193 mg, 0.5 mmol) in dry THF (2 mL). $(N\text{phyl})_2\text{CuLi}$ (1.5 M/diethyl ether, 0.75 mmol, 1.5 equiv.) was added slowly at -78°C . After 1.5 h the iodine-copper exchange was completed (checked by GC-MS analysis of reaction aliquots). Then propionyl chloride (185 mg, 2.0 mmol, 4 equiv.) was added. The mixture was warmed up to rt and was quenched after 3 h with saturated aqueous NH_4Cl solution and poured into water (10 mL). The aqueous phase was extracted with diethyl ether (3×20 mL). The organic fractions were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 4:1) yielded 100 mg (63% yield) of **8a** as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ = 8.70 (d, J = 1.8 Hz, 1H), 8.67 (d, J = 1.8 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.10 (q, J = 7.1 Hz, 2H), 2.65-2.54 (m, 1H), 2.60 (s, 3H), 1.58 (s, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.32-1.10 (m, 4H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ = 203.8, 200.6, 198.5, 164.6, 147.9, 138.2, 136.7, 132.8, 131.6, 129.2, 62.3, 32.2, 31.5, 19.2, 14.0, 12.9, 7.9. IR (film, cm^{-1}): 2982 (w), 2939 (w), 1725 (vs), 1448 (w), 1303 (s), 1239 (vs), 1014 (m), 908 (w), 793 (w). MS (EI, 70 ev): 301 (100), 287 (11), 273 (16), 255 (35) 231 (53). HRMS (EI): calcd. for $C_{18}H_{20}O_5$ [M^+]: 316.1311, found: 316.1305.

Ethyl 2-acetyl-3-benzoyl-5-furoylbenzoate (8b):

The reaction was carried out according to typical procedure D with ethyl 2-acetyl-3-benzoyl-5-iodobenzoate (211 mg, 1.0 mmol), $(N\text{phyl})_2\text{CuLi}$ (1.5 M/diethyl ether, 0.75 mmol, 1.5 equiv.) and 2-furoyl chloride (261 mg, 2.0 mmol, 4.0 equiv.). Standard workup and purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 10:1) yielded 126 mg (65%) of **8b** as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 300Hz): δ = 8.70 (d, J = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 7.71-7.74 (m, 2H), 7.63 (dd, J = 1.7 Hz, J = 0.8 Hz, 1H), 7.58-7.53 (m, 1H), 7.44-7.39 (m, 2H), 7.25 (d, J = 3.5 Hz, 1H), 6.56 (dd, J = 3.5 Hz, J = 1.7 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.58 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 Hz): δ = 203.9, 195.7, 180.0, 165.0, 152.3, 148.8, 148.1, 138.2, 137.0, 136.6, 134.3, 134.0, 133.7, 130.8, 129.5, 129.1, 121.6, 113.2, 62.8, 32.5, 14.4. IR (film, cm^{-1}): 3432 (vs), 2929 (w), 1721 (vs), 1654 (vs), 1596 (w), 1563(w), 1463 (m), 1449 (w), 1391(w), 1352 (w), 1275 (m),

1248(vs), 1189(w), 1013 (m), 765 (m), 707 (w). MS (EI, 70 ev): 390 (8) [M^+], 375 (100), 347 (40), 329 (10), 300 (70), 269 (75), 197 (18), 169 (15), 99 (45), 105 (50), 77 (45). HRMS (EI): calcd. for $C_{23}H_{18}O_6$ [M^+]: 390.1103, found: 390.1117.

Ethyl 2-acetyl-3-furoyl-5-crotonylbenzoate (**8c**):

The reaction was carried out according to typical procedure D with ethyl 2-acetyl-3-furoyl-5-iodobenzoate (206 mg, 0.5 mmol), $(N\text{phyl})_2\text{CuLi}$ (1.5 M/diethyl ether, 0.75 mmol, 1.5 equiv.) and *trans*-crotonyl chloride (209 mg, 2.0 mmol, 4.0 equiv.). Standard workup and purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 2:1) yielded 106 mg (60%) of **8c** as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , 300 Hz): δ = 8.58 (d, J = 1.8 Hz, 1H), 8.38 (d, J = 1.8 Hz, 1H), 7.65-7.64 (dd, J = 1.7 Hz, J = 0.8 Hz, 1H), 7.13-7.11 (dd, J = 3.5 Hz, J = 0.8 Hz, 1H), 7.10 (dd, J = 15.0 Hz, J = 7.0 Hz, 1H), 6.85 (dd, J = 15.0 Hz, J = 1.3 Hz, 1H), 6.55-6.54 (dd, J = 3.5 Hz, J = 1.7 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.58 (s, 3H), 1.98 (dd, J = 7.0 Hz, J = 1.3 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 Hz): δ = 203.8, 188.6, 181.6, 165.0, 152.0, 148.8, 148.7, 147.9, 137.9, 137.3, 130.1, 133.0, 129.5, 127.0, 122.6, 113.3, 62.8, 32.6, 19.2, 14.4. IR (film, cm^{-1}): 3403 (m), 2982 (w), 1723 (vs), 1715 (vs), 1673 (vs), 1658 (vs), 1651 (vs), 1622 (vs), 1566 (s), 1464(s), 1391(m), 1299(vs), 1243 (vs), 1212 (vs), 1171 (s), 1144 (m), 1016 (s), 966 (w), 797(m), 769 (m), 736 (m), 690 (m), 593(w). MS (EI, 70 ev): 354 (20) [M^+], 339 (40), 326 (15), 309 (17), 264 (20), 243 (100), 217 (10), 207 (30), 105 (15), 91 (20), 75 (10). HRMS (EI): calcd. for $C_{20}H_{18}O_6$ [M^+]: 354.1103, found: 354.1118.

7-Iodo-4-methyl-1-phenyl-phthalazine-5-carboxylic acid ethyl ester (**9a**):⁵

Typical Procedure E: A 10 mL flask, equipped with a magnetic stirrer, a refluxing condensor and a septum, was charged with a solution of ethyl 2-acetyl-3-benzoyl-5-iodobenzoate (84 mg, 0.2 mmol) in ethanol (5 mL). The solution was refluxed and a solution of hydrazine hydrate in ethanol (0.5 M/ethanol, 0.2 mmol, 1 equiv.) was added. The resulting mixture was refluxed for 15 min to complete the cyclization (checked by GC-MS analysis of reaction aliquots). The solution was concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 1:3) yielded 78 mg (93%) of **9a** as a white solid, mp 204 °C. $^1\text{H-NMR}$ (CDCl_3 , 300 Hz): δ = 8.40 (d, J = 1.8 Hz, 1H), 8.1 (d, J = 1.8 Hz, 1H), 7.59-7.49 (m, 5H), 4.45 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), 2.89 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 75Hz): δ = 168.1, 157.8, 155.3, 140.9, 138.2, 136.0, 133.0, 130.5, 130.0, 129.2, 127.3, 122.6, 97.3, 63.4, 23.0, 14.4. IR (film, cm^{-1}): 3426 (m), 2981 (w), 1726 (vs), 1576 (s), 1445 (m), 1388(m), 1361 (m), 1281 (vs), 1180 (vs), 1014 (m), 891 (w), 834 (w), 766 (m), 703 (s), 587 (w). MS (EI, 70 ev): 418 (100) [M^+], 389 (40), 373 (25), 344 (5), 331 (5), 317 (5), 291 (30), 263 (80), 189 (60), 163 (20), 94 (13), 77 (10). HRMS (EI): calcd. for $C_{18}H_{15}I\text{N}_2\text{O}_2$ [M^+]: 418.0178, found: 418.0152.

1-Furan-2-yl-7-iodo-4-methyl-phthalazine-5-carboxylic acid ethyl ester (**9b**)

The reaction was carried out according to typical procedure E with ethyl 2-acetyl-3-furoyl-5-iodobenzoate (411 mg, 0.5 mmol), and hydrazine hydrate (0.5 M/ethanol, 0.5 mmol, 1 equiv.). Standard workup and purification by flash chromatography (SiO_2 , *n*-pentane/diethyl ether = 3:1) yielded 184 mg (90% yield) of **9b** as a white solid, mp 152 °C. $^1\text{H-NMR}$ (CDCl_3 , 300 Hz): δ = 9.19 (d, J = 1.8 Hz, 1H), 8.1 (d, J = 1.8 Hz, 1H), 7.59-7.49 (m, 5H), 7.71-7.70 (dd, J = 1.7 Hz, J = 0.8 Hz, 1H), 7.35-7.33 (dd, J = 3.5 Hz, J = 0.8 Hz, 1H), 6.61-6.59 (dd, J = 3.5 Hz, J = 1.7 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 2.86 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 Hz): δ = 168.1, 155.0, 151.8, 147.3, 145.5, 141.0, 137.9, 132.9, 125.7, 122.7, 114.4, 112.7, 97.6, 63.3, 23.1, 14.4. IR (film, cm^{-1}): 3434 (m), 2978 (w), 1727 (vs), 1573 (m), 1444 (w), 1392 (m), 1353 (m), 1270 (vs), 1194 (vs), 1096 (m), 1014 (m), 886 (w),

⁵ Haddadin, M. J.; Agha, B. J.; Tadri, R. F. *J. Org. Chem.* **1979**, *44*, 494.

830 (w), 758 (m), 595 (w). MS (EI, 70 eV): 408 (100) [M^+], 380 (10), 363 (25), 351 (90), 333 (10), 321 (5), 295 (10), 263 (80), 189 (60), 163 (20), 94 (13), 77 (10). HRMS (EI): calcd. for $C_{16}H_{13}IN_2O_3$ [M^+]: 407.9971, found: 407.9963.

9b