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Reactions of *ortho*-Lithiophenyl (-Hetaryl) Isocyanides with Carbonyl Compounds: Rearrangements of 2-Metalated 4*H*-3,1-Benzoxazines

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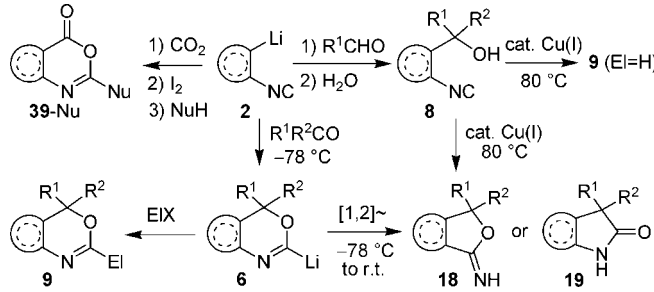

ortho-Lithiophenyl (-hetaryl) isocyanides react with aldehydes and ketones providing isocyanoalcohols **8** (36−89%, nine examples), 4*H*-3,1-benzoxazines **9** (45−78%, six examples) or, after two types of rearrangements, isobenzofuran-1(3*H*)-imines (iminophthalanes) **18** (52−75%, four examples), or indolin-2-ones **19** (42−79%, two examples), depending on the reaction conditions and substitution patterns. Isocyanoalcohols **8**, in turn, were converted to **9** or **18** under Cu(I) catalysis (66−86%, eight examples). 4*H*-3,1-Benzoxazin-4-ones **39**-Nu and isatoic anhydride **40** were obtained by the reaction of **2** with carbon dioxide followed by trapping of the lithiated intermediate with iodine and subsequent reactions with nucleophiles (45−60%, three examples).

Introduction

Aryl isocyanides represent valuable starting materials for the synthesis of quinolines,[1] indoles,[2] and other benzoannelated N-heterocycles,[3] and some of them have been used in the total syntheses of natural products.[4] Recently, we reported that *ortho*-lithiophenyl isocyanide (**2**), generated by bromine−lithium exchange on *o*-bromophenyl isocyanide, can be employed for the synthesis of 2-substituted phenyl isocyanides **1** as well as 3*H*-quinazolin-4-ones and 3*H*-quinazolin-4-thiones **3** (Scheme 1).[5] Here we report our latest results concerning the facile addition of *ortho*-lithiophenyl isocyanide (**2**) as well as *ortho*-lithiohetaryl isocyanides to aldehydes, ketones, and carbon dioxide.

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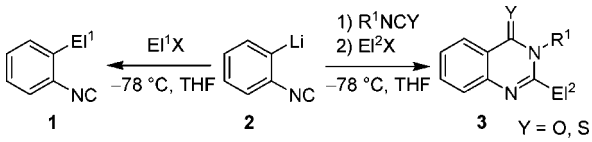
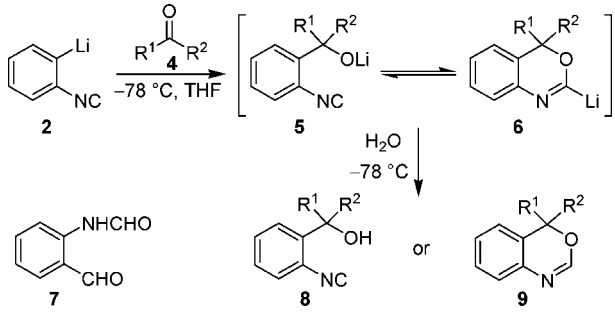
SCHEME 1. Previously Reported Utilizations of *ortho*-Lithiophenyl Isocyanide (2)[5]



Results and Discussion

Treatment of *ortho*-lithiophenyl isocyanide (**2**) with aldehydes (**4a**−**i**) at −78 °C and hydrolysis of the reaction mixture at the same temperature led to *ortho*-isocyanobenzylalcohols **8** rather than the corresponding 4*H*-3,1-benzoxazines **9** (Table 1, entries 1−9). This may be due to a predominance of the initial alkoxide adduct **5** in the equilibrium with the lithiobenzoxazine **6**. The same behavior was observed upon addition of α-metalated isocyanides and *ortho*-(lithiomethyl)phenyl isocyanides to carbonyl compounds and epoxides, which produced the respective acyclic isocyanoalcohols rather than corresponding five-, seven-, or eight-membered heterocycles **10**,[6] **11**, and **12**, respectively (Figure 1),[7] upon hydrolysis of the reaction mixture at low temperature. The reaction of **2** with ketones (**4k**−**m**), however, after hydrolysis of the reaction mixture at −78 °C, led to 4,4-disubstituted 4*H*-3,1-benzoxazines **9** in all cases (entries 11−13). This may be caused by the Thorpe−Ingold conformational effect,[8] which places the alkoxide more closely to the isocyano group and thus favors the cyclization of **5** to **6**. It might also be due to enhanced thermodynamic stability of the cyclized **6** over the noncyclized form **5** for the cases with $R^1,R^2 \neq H$. Upon treatment of **2** with dimethylformamide and subsequent addition of water, 2-(formylamino)benzaldehyde (**7**) was isolated in 76% yield, apparently arising by hydrolysis of the initially formed 4*H*-3,1-benzoxazine **9j**, as has previously been discussed.[5] Obviously, in this case, the NMe_2 donor group facilitated cyclization of **5** to **6**. Although 2-substituted 4*H*-3,1-benzoxazines are well-known compounds, simply accessible from the respective *o*-aminophenylcarbinols,[9] there is no generally applicable method for the synthesis of 2-unsubstituted heterocycles of type **9**.[10]

TABLE 1. Reaction of 1a with Aldehydes and Ketones Succeeded by Quenching with Water at −78 °C



Entry	Carbonyl Compound **4**	R^1	R^2	Product	Yield[a] (%)
1	**a**	Ph	H	**8a**	84
2	**b**	4-$MeOC_6H_4$	H	**8b**	83
3	**c**	4-ClC_6H_4	H	**8c**	89
4	**d**	4-pyridyl	H	**8d**	82
5	**e**	2-(5-methylthienyl)	H	**8e**	78
6	**f**	2-(5-methylfuryl)	H	**8f**	88
7	**g**	*t*Bu	H	**8g**	80
8	**h**	iPr	H	**8h**	36
9	**i**	1-(2-methyl-2-butene-1-yl)	H	**8i**	70
10	**j**	Me_2N	H	**7**	76
11	**k**	Ph	Ph	**9k**	48
12	**l**	Ph	CF_3	**9l**	78
13	**m**	Me	Me	**9m**	52

[a] Yields of isolated products.

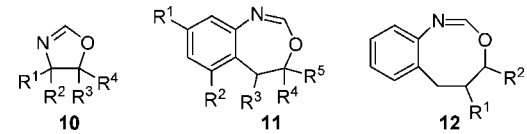


FIGURE 1. Five-, seven-, and eight-membered heterocycles previously obtained by reactions of metalated isocyanides with aldehydes, ketones, and epoxides.[6,7]

Yields of the final products **8** and **9**, respectively, were high from all nonenolizable aldehydes and ketones except for **9k** from benzophenone (**4k**), which has two large substituents that might sterically encumber the addition of **2** (entry 11). The yields of **8h** from isobutyraldehyde (**4h**) and of **9m** from acetone (**4m**) were significantly lower, probably because **2** can abstract a proton from **4h** and **4m** in competition with adding to them (entries 8 and 13). The reaction of *ortho*-lithiophenyl isocyanide **2** with 3-methylbut-2-enal (**4i**) afforded the 1,2-adduct **8i** in 70% yield without a trace of the 1,4-addition product (entry 9). Unsaturated alcohols of type **8i**, previously prepared by addition of substituted vinylmagnesium bromides to *N*-(*o*-acylphenyl)-formamides, have been shown to undergo a Lewis acid-catalyzed cyclization followed by rearrangement to 1-formyl-1,2-dihydroquinoline derivatives.[11]

The adducts of *ortho*-lithiophenyl isocyanide (**2**) to carbonyl compounds **4** can also be trapped with electrophiles other than water (Table 2). Thus, the initial adduct of **2** to pyridine-4-carbaldehyde (**4d**) upon treatment with methyl chloroformate afforded the acyclic mixed methyl carbonate **8d**-CO_2Me in 56% yield (entry 1), while the adduct to 1,1,1-trifluoroacetophenone (**4l**) was trapped with methyl chloroformate and ethyl bromoacetate to furnish the 2-substituted 4*H*-3,1-benzoxazines **9l**-CO_2Me (45%) and **9l**-CH_2CO_2Et (47%), respectively (entries 2 and 3). Addition of iodine to the same reaction mixture from **2** and **4l** and subsequent aqueous workup gave the oxo derivative **13l** (77% yield, entry 4). The initially formed 2-iodo-4-phenyl-4-(trifluoromethyl)-4*H*-benzo[1,3]oxazine (**9l**-I) apparently undergoes rapid nucleophilic substitution by water and enol to ketone tautomerization during the workup procedure and/or

(6) (a) Schöllkopf, U.; Gerhart, F.; Hoppe, I.; Harms, R.; Hantke, K.; Scheunemann, K.-H.; Eilers, E.; Blume, E. *Justus Liebigs Ann. Chem.* **1976**, 183–202. (b) Böll, W A.; Gerhart, A.; Nürrenbach, A.; Schöllkopf, U. *Angew. Chem.* **1970**, *82*, 482−483; *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 458−459. (c) Schöllkopf, U.; Böhmes, P. *Angew. Chem.* **1971**, *83*, 490−491; *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 491−492.

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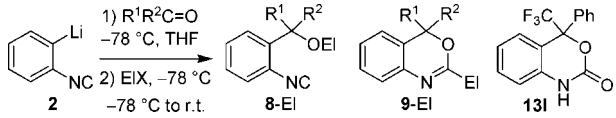
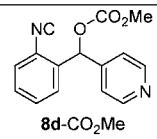
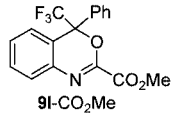
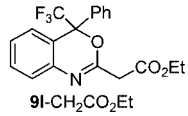
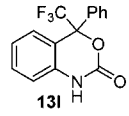
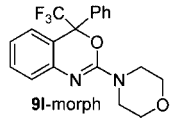
TABLE 2. Reaction of 2 with Carbonyl Compounds 4 and Trapping of the Metalated Intermediates with Electrophiles Other than Water



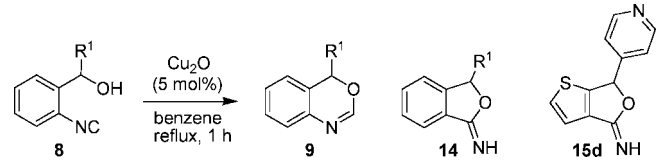
Entry	Carbonyl Compound 4	R^1	R^2	Electrophile EIX	Product	Yield (%)
1	**d**	4-Py	H	MeO_2CCl	 **8d**-CO_2Me	56
2	**l**	Ph	CF_3	MeO_2CCl	 **9l**-CO_2Me	45
3	**l**	Ph	CF_3	EtO_2CCH_2Br	 **9l**-CH_2CO_2Et	47
4	**l**	Ph	CF_3	I_2, then H_2O[a]	 **13l**	77
5	**l**	Ph	CF_3	I_2, then morpholine[b]	 **9l**-morph	55

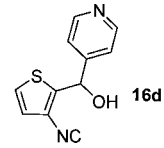
[a] Aqueous workup procedure. [b] Morpholine was added before aqueous workup.

column chromatography on silica gel. The analogous 2-chloro derivative (**9l**-Cl), generated by treatment of the adduct of **2** to **4l** with *N*-chlorosuccinimide as an electrophile, also could not be isolated and afforded **13l**. The same reaction mixture from **2**, **4l**, and iodine upon treatment with morpholine prior to the aqueous workup afforded 2-morpholinylbenzoxazine **9l**-morph in 55% yield (entry 5).

The isocyanobenzylalcohols **8** with $R^2 = H$ obtained from **2** and aldehydes were found to undergo cyclization to the corresponding 4*H*-3,1-benzoxazines **9** under Cu_2O catalysis in high yields (Table 3, entries 1−5) in the same way, as it had previously been demonstrated for the synthesis of 4,5-dihydro-3,1-benzoxazepines **11** and 4*H*-5,6-dihydro-3,1-benzoxazocines **12**.[7] Treatment of the isocyanobenzylalcohols **8** with bases such as DBU and KO*t*Bu was less effective, although it also led to the target 4*H*-3,1-benzoxazines **9**. Such 2-unsubstituted compounds turned out to be unstable in acidic as well as in basic media but could be isolated by flash chromatography on silica gel pretreated with triethylamine. In the cases of the isocyanobenzylalcohols **8f**, **8h**, and **16d** (the latter was used in the cyclization step directly after its formation from 3-isocyano-2-lithiothiophene (**21**) and pyridine-4-carbaldehyde (**4d**) without purification by column chromatography), the arene-annelated tetrahydrofuranimines **14f**,**h** and **15d**, respectively, were obtained unexpectedly as the sole products. Products of this type

TABLE 3. Cu_2O-Catalyzed Cyclization of Isocyanobenzylalcohols 8



Entry	Isocyanoalcohol	R^1	Product	Yield (%)
1	**8a**	Ph	**9a**	86
2	**8b**	4-$MeOC_6H_4$	**9b**	74
3	**8c**	4-ClC_6H_4	**9c**	75
4	**8d**	4-pyridyl	**9d**	73
5	**8g**	*t*Bu	**9g**	83
6	**8f**	2-(5-methyl-furyl)	**14f**	66
7	**8h**	iPr	**14h**	68
8	 **16d**		**15d**	74[a]

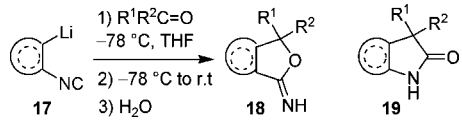
[a] Total yield for addition and subsequent cyclization, the crude isocyanoalcohol **16d** was used for the transformation without purification.

and indolin-2-ones **19** were also formed upon warming to ambient temperature of the reaction mixtures after the addition of *ortho*-lithiophenyl isocyanide (**2**) and *ortho*-lithiohetaryl isocyanides **21** and **24** to various carbonyl compounds (Table 4). The latter two organolithium reagents were generated with equal ease as **2** from the corresponding bromohetaryl isocyanides.

Apparently, the lithiated intermediates of type **6** can undergo ring contraction to form the lithiated precursors of **18** or **19** upon warming to ambient temperature of the reaction mixture obtained after addition of lithiated isocyanides **17** to carbonyl compounds. All three compounds of type **6** with trifluoromethyl substituents obviously rearranged to iminophthalanes **14o** and its heteroanalogues **23l** and **25l**, respectively (Table 4). The other examples only furnished indolin-2-ones **20n**,**k** and **22k**, respectively. Compound **20n** was isolated after the reaction of **2** with pyridine-2-carbaldehyde (**4n**) and subsequent treatment of the reaction mixture with water at −78 °C. In this case, the coordination of lithium by the pyridyl nitrogen may have played a crucial role in shifting the equillibrium from **5** to **6** and facilitate the rearrangement to the lithiated precursor of **19**. Indolin-2-ones (2-oxoindoles) of type **20** represent an important class of heterocycles with a wide range of biological activities,[12]

(12) (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432–3435. (b) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105–2108. (c) Luk, K. C.; So, S. S.; Zhang, J.; Zhang, Z. (F. Hoffman-LaRoche AG), WO 2006/136606 A3, 2006. (d) Hewawasam, P.; Gribkoff, V. K.; Pendri, Y.; Dworetzky, S. I.; Meanwell, N. A.; Martinez, E.; Boissard, C. G.; Post-Munson, D. J.; Trojnacki, J. T.; Yeleswaram, K.; Pajor, L. M.; Knipe, J.; Gao, Q.; Perrone, R.; Starrett, J. E., Jr. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023–1026. (e) Sarges, R.; Howard, H. R.; Koe, K.; Weissman, A. *J. Med. Chem.* **1989**, *32*, 437–444.

TABLE 4. Addition of *ortho*-Lithioaryl Isocyanides to Aldehydes and Ketones with Subsequent Rearrangement



o-Lithiated Aryl Isocyanide	Carbonyl Compound **4**	R^1	R^2	Product	Yield (%)
2	**n**	2-pyridyl	H	**20n**	79[a]
2	**o**	Me	CF_3	**14o**	58
2	**k**	Ph	Ph	**20k**	42
21	**k**	Ph	Ph	**22k**	52
21	**l**	Ph	CF_3	**23l**	75
24	**l**	Ph	CF_3	**25l**	64

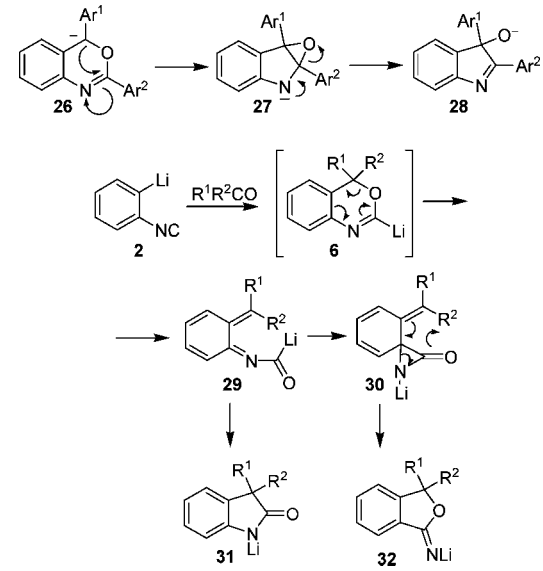
[a] Reaction mixture was treated with H_2O at −78 °C.

while only a few isobenzofuran-1(3*H*)-imines (iminophthalanes) of type **14** have been described previously.[13]

The only known ring contraction of 2,4-diaryl-substituted 4*H*-3,1-benzoxazines with formation of 3*H*-indol-3-ols proceeds in strongly basic media and was rationalized mechanistically as an intramolecular nucleophilic addition of 4-deprotonated benzoxazine **26** followed by epoxide opening (Scheme 2).[14] However, the above-mentioned benzotetrahydrofuranimines and indolin-2-ones obviously cannot be formed in such a way. Formally, the isobenzofuranimine of type **14** and the indolin-2-one of type **20**, respectively, could arise from the initially formed 2-lithium 4*H*-3,1-benzoxazine of type **6** by a [1,2]-migration of the aryl group next to nitrogen or of the alkyl group next to the oxygen atom and subsequent protonation.

Rearrangements with [1,2]-migration of an alkyl group from an oxygen and from a quaternary nitrogen atom to an adjacent

SCHEME 2. Known Ring Contraction of 2,4-Diaryl-3,1-benzoxazines[14] and Proposed Mechanism for the Reaction of 2 with Ketones



carbanion center have been known for quite some time as Wittig[15] and Stevens rearrangements,[16] respectively. Yet, the stereoelectronic requirements make such [1,2]-migrations unlikely in the case of **6**. More probably, the intermediate **6** undergoes a pericyclic ring opening to yield **29**, which by intramolecular 1,4-addition would furnish the lithiated indolin-2-one **31** or by intramolecular 1,2-addition and subsequent 6π-pericyclic reaction of the resulting **30** provide the lithiated isobenzofuranimines **32** (Scheme 2).[17]

On the other hand, in the Cu_2O-catalyzed transformations of isocyanobenzylalcohols **8** to **9** and **14**, the process starts with the coordination of an isocyano group to the Cu(I) species, and this is succeeded by nucleophilic addition of the hydroxyl group to the thus activated isocyano group in **33** to yield, after deprotonation, the metalated 4*H*-3,1-benzoxazine **34** (Scheme 3). The latter rearranges just like **6** to provide the deprotonated isobenzofuran-1(3*H*)-imine **35** which, by protonation, gives **14**. Alternatively, the intermediate **34** can be protonated directly to yield the 4*H*-3,1-benzoxazine **9** as was also observed experimentally. The transformation of **33** to **34** should not be regarded as an isocyanide insertion into an O−H bond[18] because the product of such a process, the 4*H*-3,1-benzoxazine **9**, is not converted to **14** under the same reaction conditions, as was confirmed by a control experiment.[19] Interestingly, the predominant formation of **9** or **14** from **8** is intricately controlled by the type of substitution. Thus, **8h** (R^1 = *i*Pr, R^2 = H) gave the isobenzofuran-1-(3*H*)-imine **14h**, while **8g** (R^1 = *t*Bu, R^2

(13) For some syntheses of iminophthalanes, see: (a) Sato, R.; Ohmori, M.; Kaitani, F.; Kurosawa, A.; Senzaki, T.; Goto, T.; Saito, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2481–2485. (b) Suzuki, H.; Koge, M.; Inoue, A.; Hanafusa, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1168–1171. (c) Suzuki, H.; Koge, M.; Hanafusa, T. *J. Chem. Soc., Chem. Commun.* **1977**, 341–342.

(14) (a) Lednicer, D.; Emmert, E. D. *J. Heterocycl. Chem.* **1970**, *7*, 575–581. (b) Schmidt, R. R.; Beitzke, B. *Chem. Ber.* **1983**, *116*, 2115–2135.

(15) For reviews on [1,2]-Wittig rearrangement, see: (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann./Recueil* **1997**, 1275–1281. (b) Tomooka, K. In *The Chemistry of OrganolithiumCompounds*; Rappoport, Z., Marek, I., Eds.; Wiley: London, 2004; Vol. 2, pp 749−828.

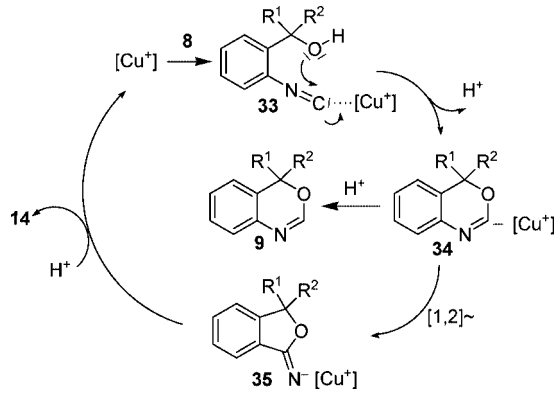
(16) For reviews, see: (a) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043–1062. (b) Markó, I. E., Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 3, pp 913−973.

(17) The authors are grateful to one of the reviewers who pointed out this possibility.

(18) (a) Saegusa, T.; Ito, Y. *Synthesis* **1975**, 291–300. (b) Saegusa, T.; Ito, Y.; Takeda, N.; Hirota, K. *Tetrahedron Lett.* **1967**, *8*, 1273–1275. (c) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K. *Tetrahedron Lett.* **1967**, *8*, 521–524.

(19) A mixture of **9l** in benzene with 10 mol % of Cu_2O was heated under reflux for 1 h. No changes were detected according to TLC.

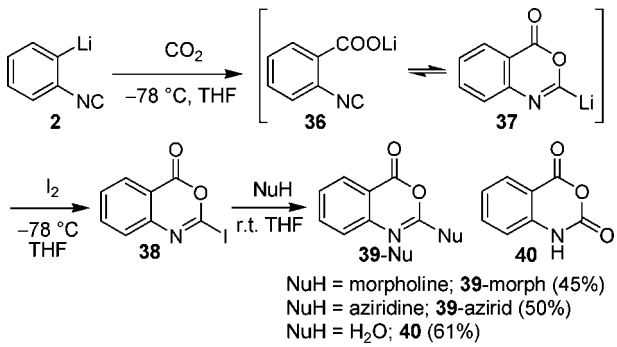
SCHEME 3. Mechanism of the Cu_2O-Catalyzed Cyclization of Isocyanobenzylalcohols 8



= H) provided the corresponding benzoxazine **9g** exclusively. The isocyanobenzylalcohols **8f** and **16d** with furyl and thienyl moieties afforded selectively isobenzofuran-1-(3*H*)-imine **14f** and thiophene-annelated tetrahydrofuranimine **15d**, respectively, whereas all the other aryl-substituted isocyanobenzylalcohols **8a**−**8d** gave the corresponding 4*H*-3,1-benzoxazines **9**.

ortho-Lithiophenyl isocyanide **2** also reacts with carbon dioxide at −78 °C to initially yield lithium *ortho*-isocyanobenzoate **36**, which equilibrates with the 2-lithiobenzoxazin-4-one **37**. The latter reacts with iodine to furnish 2-iodobenzoxazin-4-one (**38**) which readily undergoes in situ substitution by added nucleophiles such as water, morpholine, and aziridine to provide the correspondingly substituted 4-*H*-benzo[3,1]oxazin-4-ones[20,21] **39**-Nu and isatoic anhydride **40** in a one-pot four-step procedure in moderate yields (Scheme 4).

SCHEME 4. Synthesis of 2-Substituted 4*H*-Benzo[*d*][1,3]oxazin-4-ones (39-Nu) and Isatoic Anhydride 40



In conclusion, the reactions of *ortho*-lithiophenyl isocyanide and other *ortho*-lithiohetaryl isocyanides with aldehydes, ketones, and carbon dioxide furnish, apart from the expected isocyanobenzylalcohols **8**, 4*H*-3,1-benzoxazines **9**, and 4*H*-benzoxazin-4-ones **39**-Nu, iminophthalanes of type **18** or indolin-2-ones of type **19**, respectively, by two novel rearrangements of the intermediate 2-lithio-4*H*-3,1-benzoxazines.

(20) For examples of naturally occurring 4*H*-3,1-benzoxazin-4-ones, see: (a) Mason, J. J.; Bergman, J.; Janosik, T. *J. Nat. Prod.* **2008**, *71*, 1447–1450. (b) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432–2433.

(21) (a) Fenton, G.; Newton, C. G.; Wyman, B. M.; Bagge, P.; Dron, D. I.; Riddell, D.; Jones, G. D. *J. Med. Chem.* **1989**, *32*, 265–272. (b) Hedstrom, L.; Moorman, A. R.; Dobbs, J.; Abeles, R. H. *Biochemistry* **1984**, *23*, 1753–1759. For reviews on 4*H*-3,1-benzoxazin-4-ones, see: (c) Coppola, G. M. *J. Heterocycl. Chem.* **1999**, *36*, 563–588. (d) Coppola, G. M. *J. Heterocycl. Chem.* **2000**, *37*, 1369–1388.

Experimental Section

General Procedure for the Reaction of *ortho*-Lithiophenyl (-Hetaryl) Isocyanides with Aldehydes and Ketones (GP1). To a solution of *o*-bromophenyl (-hetaryl) isocyanide (2 mmol) in anhydrous tetrahydrofuran (20 mL), kept in an oven-dried 25 mL Schlenk flask under an atmosphere of dry nitrogen, was added dropwise with stirring a 2.5 M solution of *n*-BuLi in hexane (0.8 mL, 2 mmol) at −78 °C over a period of 10 min. The mixture was stirred at −78 °C for another 10 min, before the respective aldehyde (ketone) (2 mmol) in anhydrous THF (2 mL) was added dropwise. The mixture was stirred at −78 °C for 3 h and was then treated in three different ways (variants A−C).

(A) The reaction was quenched with water (2 mL) at −78 °C.

(B) The mixture was gradually warmed to 0 °C within 2 h, and then the reaction was quenched with water (2 mL) at 0 °C.

(C) The mixture was treated with the solution of an electrophile in THF (2 mL) at −78 °C, and the resulting mixture was stirred at the same temperature for 2 h and warmed to rt overnight.

Then the mixture was diluted with diethyl ether (50 mL), washed with water (2 × 10 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure to give a crude product, which was purified by column chromatography on silica gel or by Kugelrohr distillation.

(2-Isocyanophenyl)(phenyl)methanol (8a). The isocyanide **8a** (350 mg, 84%) was obtained from *o*-bromophenyl isocyanide (364 mg, 2 mmol) and benzaldehyde (**4a**) (212 mg, 2 mmol) following GP1 (A) and after column chromatography (hexane/ethyl acetate 4:1, R_f = 0.27) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 7.9 Hz, 1 H, Ar−H), 7.47−7.25 (m, 8 H, Ar−H), 6.18 (s, 1 H, CH), 2.51 (s, 1 H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$, APT) δ 167.6 (C), 141.6 (C), 139.9 (C), 129.7 (CH), 128.7 (2 CH), 128.3 (CH), 128.2 (CH), 127.0 (2 CH), 126.9 (2 CH), 124.4 (C), 71.9 (CH); IR (film) 3393 (br, OH), 3064, 3031, 2896, 2120 (NC), 1483, 1453, 1188, 1035, 1024, 761, 699 cm^{-1}; MS (EI) *m*/*z* (%) 209 (46) [M$^+$], 180 (100), 77 (34); HRMS (EI) calcd for $C_{14}H_{11}NO^+$ [M]$^+$ 209.0841, found 209.0839.

3-(Trifluoromethyl)-3-methylisobenzofuran-1(3*H*)-imine (14o). The compound **14o** (250 mg, 58%) was obtained from *o*-bromophenyl isocyanide (364 mg, 2 mmol) and 1,1,1-trifluoroacetone (**4o**) (224 mg, 2 mmol) following GP1 (B) and after Kugelrohr distillation (0.1 Torr, 85−95 °C) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (td, J = 7.2, 1.9 Hz, 1 H, Ar−H), 7.30−7.21 (m, 3 H, Ar−H), 7.15 (s, 1 H, NH), 1.87 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, APT) δ 148.4 (C), 136.7 (C), 130.7 (CH), 127.9 (CH), 125.8 (CH), 125.3 (CH), 124.1 (q, J_{CF} = 287 Hz, C), 121.4 (C), 77.2 (q, J^2_{CF} = 31 Hz, C), 22.0 (CH_3); MS (EI) *m*/*z* (%) 215.0 (39) [M$^+$], 146.0 (100); IR (KBr) 3304 (br) (NH), 1676, 1636, 1456, 1295, 1225, 1179, 1096, 769 cm^{-1}. Anal. Calcd for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.74; H, 3.51; N, 6.30.

Methyl 4-(Trifluoromethyl)-4-phenyl-4*H*-3,1-benzoxazine-2-carboxylate (9l-CO_2Me). Compound **9l**-CO_2Me (302 mg, 45%) was obtained from *o*-bromophenyl isocyanide (376 mg, 2 mmol), 1,1,1-trifluoroacetophenone (**4l**) (348 mg, 2 mmol), and methyl chloroformate (189 mg, 2 mmol) following GP1 (C) and after column chromatography on silica gel (hexane/ethyl acetate 4:1, R_f = 0.26) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 4 H, Ar−H), 7.39 (m, 5 H, Ar−H), 3.98 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, APT) δ 159.3 (C), 145.6 (C), 137.0 (C), 135.0 (C), 130.7 (CH), 129.7 (CH), 129.3 (CH), 128.4 (CH), 127.4 (CH), 127.3 (CH), 126.1 (q, J = 2.3 Hz, CH), 123.4 (q, J = 285.4 Hz, C), 121.1 (C), 83.0 (q, J = 30.8 Hz, C), 53.8 (CH_3); MS (EI) *m*/*z* (%) 335 (16) [M$^+$], 266 (88), 43 (100); IR (KBr) 2955, 1745, 1647, 1601, 1327, 1293, 1211, 1180, 990, 767, 702 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{12}NF_3O_3Na^+$ [M + Na$^+$] 358.0661, found 358.0666.

General Procedure for the Cu_2O-Catalyzed Cyclization of (2-Isocyanophenyl)methanols 8 (GP2). To a solution of isocyanobenzylalcohol **8** (2 mmol) in benzene (10 mL) was added Cu_2O (14.4 mg, 5 mol %), and the resulting mixture was heated under

reflux for 1 h. Then, the mixture was cooled to rt, the solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel.

4-Phenyl-4*H*-3,1-benzoxazine (9a). Compound **9a** (301 mg, 86%) was obtained from isocyanobenzylalcohol **8a** (350 mg, 1.67 mmol) following GP2 and after column chromatography on silica gel (hexane/ethyl acetate/Et_3N 5:1:1, R_f = 0.38) as a slightly yellow solid: mp 62−63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.22 (m, 7 H, Ar−H), 7.19 (s, 1 H, CH=N), 7.12 (dt, J = 7.5, 1.5 Hz, 1 H, Ar−H), 6.73 (d, J = 7.5 Hz, 1 H, Ar−H), 6.29 (s, 1 H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.4 (CH), 139.8 (C), 137.1 (C), 129.1 (CH), 129.0 (CH), 128.7 (CH), 127.8 (CH), 127.1 (CH), 125.5 (CH), 125.3 (C), 124.8 (CH), 77.4 (CH); MS (EI) *m*/*z* (%) 209.0 (56) [M^+], 180.0 (100); IR (KBr) 1612, 1601, 1489, 1455, 1219, 1125, 1096, 773 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.71; H, 5.19; N, 6.88.

General Procedure for the Synthesis of 4*H*-3,1-Benzoxazine-4-ones 39 and Isatoic Anhydride 40 (GP3). To a solution of *o*-bromophenyl isocyanide (364 mg, 2 mmol) in anhydrous THF (20 mL), kept in an oven-dried 25 mL Schlenk flask under an atmosphere of dry nitrogen, was added dropwise with stirring a 2.5 M solution of *n*-BuLi in hexane (0.8 mL, 2 mmol) at −78 °C over a period of 10 min. The mixture was stirred at −78 °C for 10 min, and CO_2 was bubbled through the mixture at −78 °C for 1 min. The mixture was stirred at −78 °C for 1 h, then a solution of I_2 (508 mg, 2 mmol) in anhydrous THF (2 mL) was added dropwise, and the temperature was allowed to rise to 20 °C over a period of 1 h. Water (for the synthesis of **40**) or a solution of the corresponding amine (2 mmol) and triethylamine (2 mmo) in THF (2 mL) was added, and the mixture was stirred at rt for 2 h. After addition of saturated NH_4Cl solution (20 mL), the mixture was diluted with diethyl ether (50 mL), washed with $Na_2S_2O_5$ solution (20 mL), water (10 mL), and brine (20 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the crude product was purified by column chromatography on silica gel.

2-(Aziridin-1-yl)-4*H*-3,1-benzoxazin-4-one (39-azirid). Compound **39**-azirid (188 mg, 50%) was obtained following GP3 from *o*-bromophenyl isocyanide (364 mg, 2 mmol) and aziridine (86 mg, 2 mmol) and after column chromatography on silica gel (ethyl acetate, R_f = 0.26) as a colorless solid: mp 154−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, J = 7.5, 1.3 Hz, 1 H, Ar−H), 7.66 (ddd, J = 8.4, 7.2, 1.6 Hz, 1 H, Ar−H), 7.50 (d, J = 8.1 Hz, 1 H, Ar−H), 7.32 (ddd, J = 8.1, 7.2, 1.3 Hz, 1 H, Ar−H), 4.76 (t, J = 8.4 Hz, 2 H, CH_2), 4.37 (t, J = 8.4 Hz, 2 H, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.8 (C), 155.4 (C), 148.9 (C), 134.8 (CH), 126.5 (CH), 126.1 (CH), 124.7 (CH), 118.3 (C), 65.8 (CH_2), 42.2 (CH_2); MS (EI) *m*/*z* (%) 188.1 (100) [M^+], 146.1 (86); IR (KBr) 1696, 1640, 1609, 1562, 1473, 1418, 1263, 1135, 1015, 980, 863, 769, 692 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.62; H, 4.21; N, 14.67.

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Supporting Information Available: Experimental procedures and full characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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