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Application of Copper(I) Iodide/Diorganoyl Dichalcogenides to the Synthesis of 4-Organochalcogen Isoquinolines by Regioselective C–N and C–Chalcogen Bond Formation

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Abstract: A copper-catalyzed cyclization of (*ortho*-alkynyl)benzaldimines with diorganoyl dichalcogenides allowed the synthesis of 4-organochalcogen isoquinolines, whereas the presence of base in the reaction medium inhibited the product formation producing the undesirable isoquinoline without the organochalcogen atom at the 4-position. The cyclization reaction was carried out by using CuI (20%) as a catalyst with diorganoyl dichalcogenides (1.5 equiv) in the presence of DMF at 100°C. Furthermore, the reaction did not require an argon atmosphere and was carried out in an open flask. The cyclization reaction tolerated a variety of functional groups both in *ortho*-alkynylbenzaldimines and diorganoyl dichalcogenides, such as trifluoromethyl, chloro, fluorine, and methoxyl, to give the six-membered heterocyclic ring exclusively through a 6-*endo-dig* cyclization process. The organochalcogen group present at the 4-position of the isoquinoline ring was further subjected to a selective chalcogen–lithium exchange reaction followed by the addition of aldehydes to afford the desired secondary alcohols in good yields. The obtained isoquinolines also proved to be suitable substrates for the Suzuki and Sonogashira coupling conditions affording the corresponding products through C–C bond formation.

Keywords: copper iodide · cyclization · isoquininoline · selenium · tellurium

Introduction

Nitrogen-containing heterocycles are ubiquitous in natural products and bioactive molecules, and numerous studies on their chemistry and synthesis have been reported thus far.[1] Among these, isoquinoline derivatives are known to present a wide range of biological activities, and have proven to be antifungal,[2] antitumor,[3] antibacterial,[4] and antiprotozoic[5] drugs as well as antineoplastics.[6] Examples of the therapeutic potential and efficacy of biologically active isoquinoline motifs include Berberine, which has been shown to be useful as anti-cancer and anticonvulsant agent;[7] Coralyne, which has been reported as a antimicrobial, anti-tumor, anti-leukemic and anti-neoplastic agent[8] and Ribarivin, which is a selective inhibitor of enterovirus.[9]

The classical methods used for the construction of the isoquinolines framework, the Pomeranz–Fritsch,[10] Bischeler–Napieralski,[11] and Pictet–Spengler reactions,[12] require severe conditions that do not agree with an environmentally friendly concept. These reactions are often limited because of unavailability of suitably substituted and, sometimes, the requirement of strong acids in combination with high temperatures.[13] Some of these drawbacks have been overcome by the recent development in transition-metal-catalyzed cyclization reactions, which allow the construction of target heterocyclic skeletons under relatively mild conditions.[14] From the recent viewpoint of environmentally benign or green chemistry, the development of cost-effective, mild, and alternative methodologies are of considerable interest.[15] Part of our recent research in the development of the new alternative system to the cyclization of unsaturated substrates[16] revealed that a mixture of diorganoyl dichalcogenides and copper salts was a good alternative to the classical electrophilic[17] and transition-metal-based cyclizations.[18] In this context, to the best of our knowledge, there is no example of a benzaldimine cyclization promoted by copper/diorganoyl dichalcogenides. Therefore, we decided to further explore the potential of this new approach to the cyclization reaction and organochalcogen insertion onto benzaldimines to prepare 4-organochalcogen isoquinolines **2** (Scheme 1).

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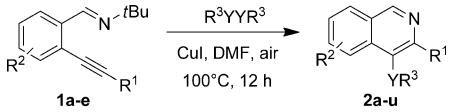
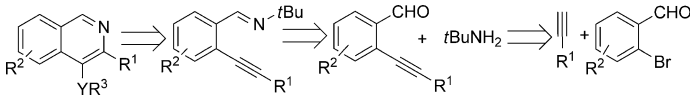


R^1, R^2 = aryl, alkyl; Y = S, Se, Te

Scheme 1. General reaction scheme.

The main advantage of our methodology is that the use of the copper/diorganoyl dichalcogenide system as the cyclizing agent generates the product with an organochalcogen group in the structure, which becomes the heterocycles useful intermediates in many processes, including transition-metal-catalyzed carbon–carbon bond formation, under relatively mild reaction conditions.[19] Moreover, there has been growing interest in the transition-metal-catalyzed reactions of organoselenium compounds and highly selective transformations of chalcogen compounds have been developed through palladium or copper catalysts.[20] Additionally, the study of organoselenium compounds as therapeutic agents has increased in the last decades due to a variety of these organochalcogens biologically active.[21] The retrosynthetic analysis to include the organochalcogen group into isoquinoline structures required the use of 2-bromobenzaldehydes, terminal alkynes and *tert*-butylamine as the starting materials and copper/diorganoyl dichalcogenide cyclization as the key step (Scheme 2).



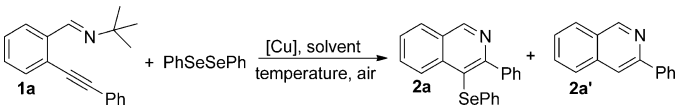
Scheme 2. Retrosynthetic analysis.

Results and Discussion

The required precursors (*ortho*-alkynyl)benzaldimines **1a–g** were synthesized in good yields by the reaction of appropriate 2-bromobenzaldehydes with terminal alkynes under Sonogashira catalysis conditions followed by the condensation reaction with *tert*-butylamine.[22]

The copper cyclization reaction was initially investigated by reacting diphenyl diselenide (1 equiv), K_2CO_3 (5 equiv) and CuI (10 mol%) in DMSO or DMF with substrate **1a** (0.25 mmol), under argon or air atmosphere, for 24 h at 100 °C. However, these reaction conditions were ineffective and the desired product **2a** was not obtained (Table 1, entries 1–3). When the reaction of (*ortho*-alkynyl)benzaldimines **1a** was carried out under the same conditions, but in the absence of a base (K_2CO_3), compound **2a** was obtained in 44% yield, followed by 30% yield of undesirable **2a′**, although a longer reaction time (24 h) was required for the complete consumption of **1a** (Table 1, entry 4). These results showed that the presence of base appears to inhibit the cyclization and induce the formation of **2a′**. The cyclization could not be improved significantly by increasing the diphenyl diselenide amount to 2 equiv, and the cyclized product **2a′**, without incorporation of PhSe in the structure, was again formed (Table 1, entry 5). However, when the reaction was performed using CuI (20 mol%), the desired isoquinoline **2a** was obtained in 72% yield, in the complete absence of **2a′** (Table 1, entry 6). Fortunately, the cyclization reaction using 1.5 equiv diphenyl diselenide and 20 mol% CuI (Table 1, entry 7) was complete in a shorter time than the same reaction using 20 mol% CuI and 1.0 equiv diphenyl diselenide (Table 1, entry 6), to give the desired product in 82% yield, without the formation of a detectable amount of **2a′**. No remarkable increase in the product yield was observed when the amount of diphenyl diselenide was increased from 1.5 to 1.2 and 2.0 equiv in the presence of 20 mol% of CuI, although the use of 1.2 equiv did afford the product **2** in the lowest yield (Table 1, entries 8 and 9). Assuming that the oxi-reducing property of diphenyl diselenide, and the consequent formation of a diphenyl diselenide–CuI complex,[23] is responsible for this cyclization process, we speculated that the cyclization reaction of (*ortho*-alkynyl)benzaldimines would be hampered under an inert atmosphere. To test our hypothesis, the reaction conditions (listed in entry 7, Table 1) were used and the reaction was carried out under argon atmosphere; as predicted, under these conditions the cyclized product was obtained in a poor yield (Table 1, entry 10). This result implies that, in the presence of oxygen, all the selenolate anion ($PhSe^-$) is oxidized to form diphenyl diselenide (PhSeSePh). These results are

Table 1. Influence of the reaction conditions in the CuI/PhSeSePh cyclization of (*ortho*-alkynyl)benzaldimines.[a]



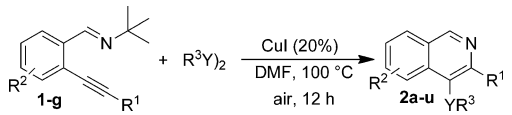
Entry	Cu source [mol%]	PhSeSePh [equiv]	Solvent	T [°C]	t [h]	Yield **2a**/**2a′** [%]
1[b,c]	CuI (10)	1	DMSO	100	24	–
2[c]	10	1	DMSO	100	24	–
3[c]	10	1	DMF	100	24	trace
4	10	1	DMF	100	24	44/30
5	10	2	DMF	100	24	52/12
6	20	1	DMF	100	24	72/–
7	20	1.5	DMF	100	12	82/–
8	20	2	DMF	100	12	80/–
9	20	1.2	DMF	100	12	68/–
10[b]	20	1.5	DMF	100	12	36/–
11	20	1.5	DMF	80	12	60/–
12	20	1.5	DMF	RT	24	trace/–
13	20	1.5	DMSO	100	24	60/–
14	20	1.5	DMA	100	12	73/–
15	20	1.5	dioxane	100	24	–
16	20	1.5	toluene	100	24	23/–
17	–	1.5	DMF	100	24	–
18	20	–	DMF	100	24	–/57
19	CuBr (20)	1.5	DMF	100	24	38
20	$CuCl_2$ (20)	1.5	DMF	100	24	31

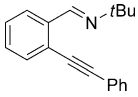
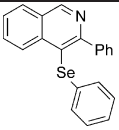
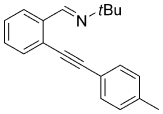
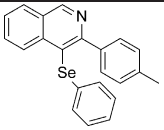
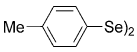
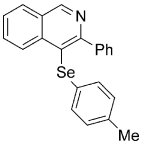
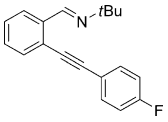
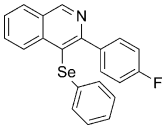
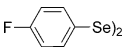
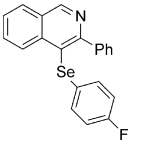
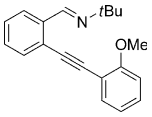
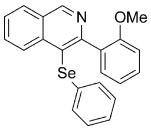
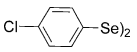
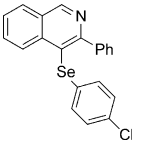
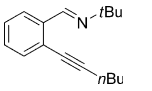
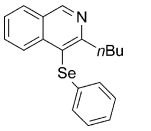
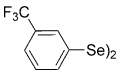
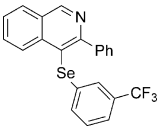
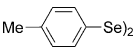
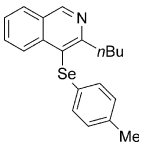
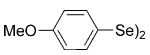
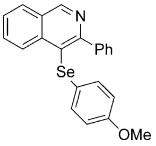
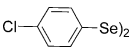
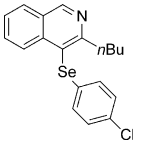
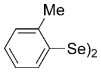
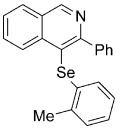
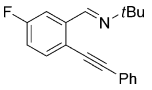
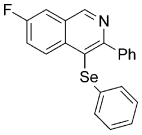
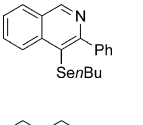
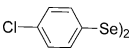
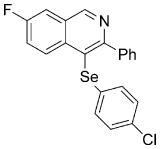
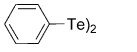
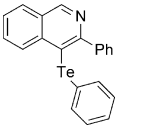
[a] Reaction conditions: (*ortho*-alkynyl)benzaldimine (0.25 mmol), diphenyl diselenide, copper salt in solvent (3 mL) under an air atmosphere. [b] An argon atmosphere was used. [c] This reaction was carried out with K_2CO_3 (5 equiv).

in agreement with other studies, which suggest that diphenyl diselenide has a clear preference for oxidative addition to copper salts.[24] The great influence of temperature on the reaction became apparent when the isoquinoline **2a** was obtained in 60% yield at 80°C, whereas only a trace of this product was detected at room temperature (Table 1, entries 11 and 12). The solvent effect was also significant in the present intramolecular cyclization (Table 1, entries 13–16). The copper salt displayed good results in polar solvents, such as DMSO and DMA (Table 1, entries 13 and 14). In contrast, dioxane and toluene gave no product or very low yield under the same conditions (Table 1, entries 15 and 16). Furthermore, both copper iodide and diphenyl diselenide played crucial roles; no desired isoquinoline **2a** was observed when either was omitted (Table 1, entries 17 and 18). As was the case for the reaction conditions with base (Table 1, entries 1–3), the use of copper iodide in the absence of diphenyl diselenide resulted in the formation of a **2a′** in 57% yield. These results are in accordance with the experiments shown in Table 1, entry 10, which suggests that a diphenyl diselenide/CuI complex should be required not only to activate the triple bond to promote the cyclization, but also as an organochalcogen source. Although the reaction with other copper salts has been examined, a lower yield of **2a** was obtained with CuBr and $CuCl_2$ (Table 1, entries 19 and 20).

On the basis of the results shown in Table 1, we undertook a systematic study applying the conditions of entry 7 to several substituted diorganoyl dichalcogenides and to different (*ortho*-alkynyl)benzaldimines to test the tolerance of functional groups as well as their effects on the conversion. These results are collected in Table 2. The yields of compounds **2** varied depending on the nature of the diorganoyl dichalcogenide. Whereas diorganoyl dichalcogenides bearing neutral, mild electron-donating, or electron-withdrawing groups on the aromatic ring provided the best yields of **2** (Table 2, entries 1 and 5), the presence of strong electron-donating group decreased the yield drastically (Table 2, entry 6). The results in Table 2 also showed that only a moderate yield of product was obtained for the cyclization between di(*o*-tolyl) diselenide and CuI, in which the steric hindrance of the *o*-tolyl group may exert significant negative effects (Table 2, entry 7). Apparently under the optimized conditions, dialkyl diselenides should exhibit a lower chemical reactivity with the copper salt than other aryl diselenides. This lower reactivity could be explained by the absence of π bonds next to the selenium atom. This is in contrast to the observed results in which dialkyl diselenide led to the cyclized product in 57% yield (Table 2, entry 8). Because of the synthetic importance of organotellurium derivatives, such as the use as substrate in palladium-catalyzed carbon–carbon bond formation[25] and synthesis of natural products,[26] we also wish to carry out the cyclization reactions of (*ortho*-alkynyl)benzaldimines with dialkyl and diaryl ditellurides. From the results shown in Table 2, it is possible to conclude that neither the dialkyl nor the diaryl group of ditellurides significantly influenced the yields of cyclized products (Table 2, entries 9–10). A number of thiol precursors were screened for the reactions with copper salts;[27] however, a few examples have been reported when a disulfide was employed as substrate.[28] As an example, the cyclization with diaryl disulfide is presented in Table 2, entry 11, which gave the cyclized product in 47% yield. To elaborate the general reactivity of the present protocol with other (*ortho*-alkynyl)benzaldimines, we substituted the phenyl group directly bonded to alkyne for alkyl and aryl substituted groups as well as adding functional groups to the main ring of (*ortho*-alkynyl)benzaldimines. The experimental results are summarized in Table 2, entries 12–14 show that there was no significant difference of reactivity between methyl, fluorine and methoxyl groups bonded to aryl group, since they gave the cyclized products equally in good yields. The latter substrate, with a methoxyl group at the *ortho* position, would give a competitive cyclization when a cyclizing agent, such as PhSeSePh/CuI, is used. Therefore, we were pleased to find that the cyclization with (*ortho*-alkynyl)benzaldimines **1d** smoothly afforded the corresponding isoquinoline **2n** through *N*-cyclization, in the complete absence of benzofuran derivatives. The ratio of products in this competitive cyclization depends on the various factors, such as electronic- (relative nucleophilicity of the functional groups, polarization of the carbon–carbon triple bond, and the cationic nature of the intermediate) and steric effects (hindrance and geometrical alignment of the functional groups), and also by the nature of the nucleophilic source. We observed that our result is in complete agreement with the study reported by Larock et al., which showed that if the substrate has a competing nitrogen and oxygen, the *N*-cyclization is predominant.[29] Furthermore, we found that the reaction with substrate **1e**, having an alkyl substituent directly bonded to the triple bond, also worked well under the standard reaction conditions; although the diaryl diselenide with a chlorine atom directly bonded to the aromatic ring gave the product in moderate yield (Table 2, entries 15–17). Finally, to examine the generality of the cyclization of (*ortho*-alkynyl)benzaldimines to 4-organochalcogen isoquinolines, two additional benzaldimines were subjected to the optimized cyclization reactions conditions. In these cases, the reaction of fluorine substituted analogue **1f** with both unsubstituted and chlorine substituted diaryl diselenides afforded the cyclized products in moderate yields (Table 2, entries 18 and 19). Similarly, benzaldimines, having a dioxole group, reacted with diphenyl diselenide and di(*p*-tolyl) diselenide to give quinolines **2t** and **2u**, in 69 and 61% yields, respectively (Table 2, entries 20 and 21). There are several examples reported in the literature in which the cyclization reactions proceed through the addition of the electrophilic source to C(sp) bonds of alkynes, followed by a nucleophilic attack giving a mixture of 5-*exo* versus 6-*endo* cyclizations.[30] The majority of theoretical and experimental studies to understand this regiochemistry suggest that it is strongly dependent on the electronic and steric effects as well as the nature of the transition-metal source. In this context, in view of the high nucleophilicity of the nitrogen atom and considering

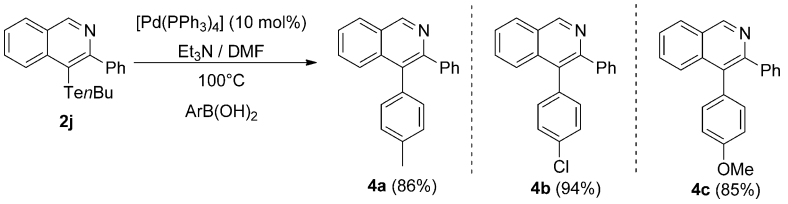
Table 2. Cyclization reactions of (*o*-alkynyl)benzaldimines mediated by CuI/diorganoyl diselenides.[a]



	(*ortho*-alkynyl)-benzaldimines	R^3YYR^3	Product	Yield [%]		(*ortho*-alkynyl)-benzaldimines	R^3YYR^3	Product	Yield [%]
1	**1a** 		**2a** 	82	12	**1b** 		**2l** 	64
2	**1a**		**2b** 	77	13	**1c** 		**2m** 	65
3	**1a**		**2c** 	74	14	**1d** 		**2n** 	66
4	**1a**		**2d** 	69	15	**1e** 		**2o** 	77
5	**1a** 		**2e** 	87	16	**1e**		**2p** 	71
6	**1a** 		**2f** 	45	17	**1e**		**2q** 	42
7	**1a** 		**2g** 	57	18	**1f** 		**2r** 	53
8	**1a**	nBuSe)$_2$	**2h** 	57	19	**1f**		**2s** 	64
9	**1a** 		**2i** 	77	20	**1g**		**2t**	69
10	**1a**	nBuTe)$_2$	**2j**	63	21	**1g**			
11	**1a**		**2k**	47				**2u**	61

[a] Reaction conditions: (*ortho*-alkynyl)benzaldimene (0.25 mmol), diorganoyl dichalcogenides (1.5 equiv), CuI (20 mol%) in DMF (5 mL) at 100 °C for 12 h under an air atmosphere.

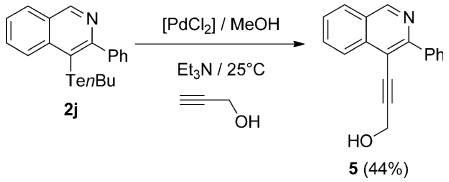
the steric effect of the *t*Bu group, our cyclization methodology showed to be highly regioselective, providing the desired isoquinoline **2**, through a 6-*endo-dig* cyclization process, as the unique regioisomer, which was confirmed by spectral data and supported by X-ray diffraction analysis (Figure 1, the Supporting Information).[31] Neither the isomeric five-membered ring products, formed through a 5-*exo-dig* process (Table 1, entry 7), nor the product involving the simple cyclization without the organochalcogen atom at the 4-position were detected under the standard conditions.



Scheme 4. Reactions of Suzuki cross-coupling.

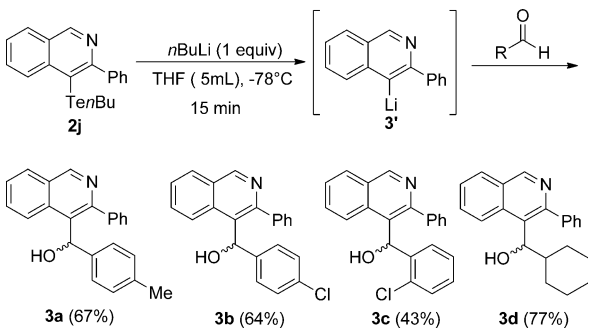
One of the most powerful applications of organotellurim compounds is the ability to undergo tellurium–lithium exchange reactions with lithium reagents. This tellurium–lithium exchange reaction proceeds very easily to give to an organolithium intermediate, which reacts with a wide range of electrophiles, providing various structures with additional functionalities.[25] As a demonstration of the usefulness of the prepared 4-organochalcogen isoquinolines, we carried out tellurium–lithium exchange reactions of 4-butyltelluro isoquinoline **2j**, followed by the reaction with aldehydes, for the formation of more functionalized isoquinolines. As expected, reaction of *n*-butyllithium (1.0 equiv) with 4-butyltelluro isoquinoline **2j** (1.0 equiv) in THF (3 mL), at −78 °C gave the lithium intermediate **3′**, which after reaction with aldehydes, afforded the corresponding secondary alcohol **3a–d** in 43–77 % yields (Scheme 3).

Recently, a new application of organotellurium compounds employing palladium-catalyzed cross-coupling was described,[19] in which they behave as aryl or vinyl carbocation equivalents and react in a manner similar to vinylic halides or triflates in the Sonogashira,[32] Heck,[33] Suzuki[34] and Stille[35] cross-coupling reactions. This led us to explore the possibility of using these 4-chalcogen isoquinolines as substrates in palladium cross-coupling reactions, under classical Suzuki and Sonogashira protocols. Under Suzuki reaction conditions, 4-butyltelluro isoquinoline **2j** underwent smooth cross-coupling upon exposure to boronic acids affording 4-aryl isoquinoline **4a–c** in excellent yields (Scheme 4). In contrast with earlier results obtained in Suzuki cross-coupling, the direct treatment of 4-butyltelluro isoquinoline **2j** with propargylic alcohol, $PdCl_2$, and Et_3N in methanol, under Sonogashira conditions, also afforded the cross-coupling product; however, even in this case, the yield of **5** was substantially lower (44 %; Scheme 5).

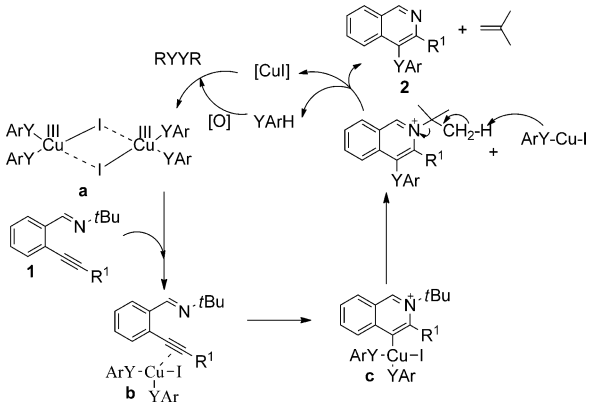


Scheme 5. Reactions of Sonogashira cross-coupling.

Based on the understanding that in the Cu^{I}-catalyzed cross coupling, copper is easily admitted as a copper complex having an oxidation state +3[24a] and that this complex could be stabilized by the selenium atom,[27a] we proposed a plausible mechanism to support the current Cu^{I}-catalyzed cyclization, as illustrated in Scheme 6. The mechanism involves the following steps: 1) The interaction of CuI with the diorganoyl dichalcogenide leads to the Cu^{III} tetracoordinated square-planar chalcogenolate **a**; 2) the alkyne coordination to the metal center provides the cationic organo-Cu^{III} complex **b**; 3) nucleophilic anti-attack of the nitrogen atom on the activated triple bond leads to the intermediate **c**; 4) reductive elimination gives the C–Se bond and anionic complex ArSeCu[36] and 5) cleavage of the *tert*-butyl group



Scheme 3. Reaction of 4-lithio isoquinoline intermediate with aldehydes.



Scheme 6. Proposed reaction mechanism.

from the nitrogen releases the 4-organochalcogen isoquinolines **2** and chalcogenol species (ArYH), which is oxidized under an air atmosphere, regenerating dichalcogenide and CuI in the catalytic cycle. The competing processes is the cyclization of the starting material to afford the isoquinoline **2a′**, without incorporation of PhSe in the structure, promoted by a hydrogen transfer to the intermediate **c**.

Conclusion

A catalytic approach to 4-(organochalcogen)isoquinolines of potential interest has been developed through the intramolecular cyclization of (*ortho*-alkynyl)benzaldimines with diorganoyl dichalcogenides under copper catalysis. A detailed study related to the effect of the reaction conditions on product distribution was carried out. The results showed that the presence of base in the medium inhibited the product formation releasing the undesirable isoquinoline without the organochalcogen at the 4-position. By contrast, the cyclization carried out in the absence of base under air atmosphere afforded 4-(organochalcogen)isoquinoline exclusively through a 6-*endo-dig* cyclization process. The optimized conditions worked well with a broad range of (*ortho*-alkynyl)-benzaldimines and diorganoyl dichalcogenides to afford the corresponding products with high regioselectivity and in good yields. The presence of an organochalcogen substituent in the isoquinoline structure allowed further structural elaboration through conversion of the chalcogen group into other substituents. For example, when the compound **2j** was applied to the tellurium–lithium exchange conditions, followed by reaction with aldehydes, the corresponding secondary alcohols were obtained in high yields. Furthermore, we have also successfully applied the isoquinoline **2j** as a substrate in Suzuki and Sonogashira coupling conditions affording the corresponding products through C–C bond formation in moderate to good yields. In addition, all the compounds prepared in this manuscript are solids or oils, completely odorless, and very stable, which can be purified and stored in the lab in a simple flask for more than one month.

Experimental Section

General procedure for the CuI-catalyzed cyclization: The appropriate diorganoyl dichalcogenide (0.375 mmol; 1.5 equiv) was added to a solution of DMF (3 mL) and CuI (20 mol%) under an air atmosphere. The resulting solution was stirred for 15 min at room temperature. Next, the appropriate *ortho*-alkynylbenzaldimines (0.25 mmol) in DMF (2 mL) was added and the resulting solution was heated at 100 °C for 12 h. After this, the solution was cooled to room temperature, diluted with ethyl acetate (10 mL), and washed with saturated aq. $NaHCO_3$ (3×10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane (1:20) as eluent to give **2a** (0.074 g, 82%) as a pale yellow solid.

3-Phenyl-4-(phenylselenyl)isoquinoline (**2a**): M.p 112–114 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.34 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.75–7.53 (m, 4H), 7.43–7.36 (m, 3H), 7.10–1.00 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 158.5, 153.2, 142.1, 138.5, 133.1, 131.7, 129.8, 129.6, 129.1, 128.6, 128.2, 128.0, 128.0, 127.6, 127.4, 126.1, 121.3 ppm; MS (EI, 70 eV): *m/z* (relative intensity): 361 (76), 284 (100), 280 (69), 203 (33), 176 (60), 127 (5), 77 (27), 51 (19); elemental analysis calcd (%) for $C_{21}H_{15}NSe$: C 70.00; H 4.20; found: C 70.23, H 4.28.

General procedure for the reaction of intermediate 3-phenyl-4-lithioisoquinoline with *n*BuLi: *n*BuLi (0.25 mmol, of a 2.5 M solution in hexane) was added (in one portion) to a two-necked round-bottomed flask, under argon, containing a solution of **2j** (0.25 mmol) in THF (3 mL) at −78 °C. The reaction mixture was stirred for 15 min, and then a solution of the appropriated aldehyde (0.3 mmol) in THF (2 mL) at −78 °C was added. The reaction mixture was allowed to stir at room temperature for 2 h. After this, the mixture was diluted with ethyl acetate (20 mL) and washed with a saturated solution of NH_4Cl (20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography and eluted with ethyl acetate/hexane to give **3a** (0.055 g, 67%) as a white solid.

(3-Phenylisoquinolin-4-yl)(p-tolyl)methanol (**3a**): M.p. 146–148 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.08 (s, 1H), 8.11–8.06 (m, 1H), 7.92–7.88 (m, 1H), 7.54–7.38 (m, 4H), 7.30 −7.05 (m, 8H), 6.39 (s, 1H), 3.74 (sl, 1H) 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.1, 140.6, 140.1, 136.3, 134.7, 130.0, 129.2, 128.9, 128.6, 128.1, 128.0, 127.8, 127.1, 126.7, 125.9, 71.6, 21.0 ppm; MS (EI, 70 eV): *m/z* (relative intensity): 325 (82), 238 (20), 207 (100), 73 (60); elemental analysis calcd (%) for $C_{23}H_{19}NO$: C 84.89; H 5.89; found: C 84.96, H 5.92.

General procedure for the Suzuki–Miyaura cross-coupling reaction: Triethylamine (2 equiv), was added to a suspension of 4-(buthyltelluro)-3-phenylisoquinoline (**2j**) (0.098 g, 0.25 mmol), boronic acid (1.5 equiv), [$Pd(Ph_3P)_4$] (10 mol%) and silver(I) oxide (1 equiv) in DMF (3 mL) and the reaction mixture was heated to reflux for 90 min with stirring, then cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was washed with saturated solution of NH_4Cl (2×10 mL) and water (2×10 mL), dried over $MgSO_4$, and concentrated under vacuum. Purification by silica gel chromatography (eluting with hexane/ethyl acetate 9.0:1.0) yielded **4a** (0.063 g, 86%) as white solid.

3-Phenyl-4-p-tolylisoquinoline (**4a**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.35 (s, 1H), 8.04–7.98 (m, 1H), 7.72–7.65 (m, 1H), 7.62–7.53 (m, 2H), 7.41–7.35 (m, 2H), 7.27–7.09 (m, 7H), 2.38 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.5, 150.3, 140.9, 136.9, 136.1, 134.1, 131.0, 130.6, 130.3, 130.2, 128.9, 127.5, 127.4, 127.4, 126.9, 126.7, 125.6, 21.2 ppm; MS (EI, 70 eV): *m/z* (relative intensity): 294 (100), 179 (11), 139 (23), 73 (8); elemental analysis calcd (%) for $C_{22}H_{17}N$: C 89.46; H 5.80; found: C 89.65, H 5.86.

General procedure for the Sonogashira cross-coupling reaction: Compound **2j** (25 mmol) was added to a two-necked round-bottomed flask (25 mL) under an argon atmosphere containing [$PdCl_2$] (20 mol%), CuI (20 mol%) and dry methanol (3 mL). After stirring the mixture for 5 min at room temperature, propargyl alcohol (0.5 mmol) and Et_3N (0.25 mL) were added. The reaction was stirred at room temperature for 6 h. After this time the solid part was filtered under vacuum. Brine was then added to the filtrate and the solution was extracted with dichloromethane (3× 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (70:30) to give **5** (0.029 g, 44%) as light yellow solid.

3-(3-phenylisoquinolin-4-yl)prop-2-yn-1-ol (**5**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.26 (s, 1H), 8.37–8.33 (m, 1H), 8.04–7.97 (m, 3H), 7.82–7.71 (m, 1H), 7.67–7.60 (m, 1H), 7.52–7.38 (m, 3H), 4.55 (s, 2H), 2.04 ppm (sl, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.6, 151.7, 139.8, 136.8, 131.4, 129.8, 128.6, 127.9, 127.8, 127.6, 126.5, 111.9, 97.3, 81.7, 51.8 ppm; MS (EI, 70 eV): *m/z* (relative intensity): 259 (29), 206 (100), 132 (13), 73 (32); HRMS (ESI): *m/z* calcd for $C_{18}H_{13}NO$: 259.0997 [*M*+H]; found: 259.1004.

Acknowledgements

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Cyclization

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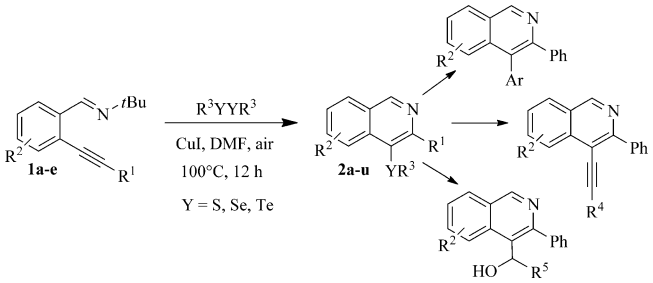
Application of Copper(I) Iodide/ Diorganoyl Dichalcogenides to the Synthesis of 4-Organochalcogen Isoquinolines by Regioselective C–N and C–Chalcogen Bond Formation



Copper-catalyzed cyclization of (*ortho*-alkynyl)benzaldimines with diorganoyl dichalcogenides enabled the synthesis of 4-organochalcogen isoquinolines (see scheme). The cyclization reaction tolerated a variety of functional groups both in the (*ortho*-alkynyl)benzaldimines and the diorganoyl dichalcogenides, such as trifluoromethyl, chloro, fluoro and methoxyl, to give the six-membered heterocycle through a 6-*endo-dig* cyclization process.

