

## Iodine-Mediated Electrophilic Cyclization of 2-Alkynyl-1-methylene Azide Aromatics Leading to Highly Substituted Isoquinolines and Its Application to the Synthesis of Norchelerythrine

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**Abstract:** The reaction of 2-alkynyl-1-methylene azide aromatics **1** with iodine and/or other iodium donors, such as the Barluenga reagent ( $\text{Py}_2\text{IBF}_4/\text{HBF}_4$ ) and NIS, gave highly substituted cyclization products, namely, the 1,3-disubstituted 4-iodoisoquinolines **2**, in good to high yields. Not only simple 2-alkynyl benzyl azides **1a–j** and their substituted analogues **1k–u** and **6** but also heteroaromatic analogues, including pyridine **8**, pyrroles **10a–c**, furane **10d**, and thiophenes **10e–g**, gave the corresponding isoquinoline derivatives in excellent to allowable yields. Electron-donating and electron-accepting substituents on the aromatic ring were equally tolerated, and either acidic or basic (or even neutral) reaction conditions, depending on the reactivity of the substrate, could be applied to smoothly convert the azide starting materials into the desired isoquinoline products in moderate to good yields. Limits were found only in connection with the substituent at the alkyne terminus, where electron-neutral or electron-donating substituents are clearly favored. The iodine-mediated electrophilic cyclization of **1** most probably proceeds through the iodonium ion intermediate **4** followed by nucleophilic cyclization of the azide and subsequent elimination of  $\text{N}_2$ . This new methodology was successfully applied to the short synthesis of norchelerythrine.

### Introduction

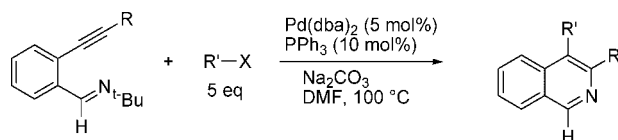
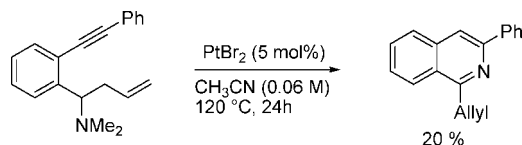
Isoquinoline and heterocyclic pyridine derivatives are an important class of alkaloids, commonly found in natural products.<sup>1</sup> Because of their biological activities, they are often used as building blocks in pharmaceutical compounds.<sup>2</sup> Furthermore, they are utilized as chiral ligands for transition-metal catalysts,<sup>3</sup> and their iridium complexes are used in organic light-emitting diodes.<sup>4</sup> For delicate and sophisticated natural product

synthesis, as well as for fine-tuning of the biological and/or physical properties of those compounds for final application, a general and flexible approach to this class of heterocycles that tolerates a wide variety of functional groups is highly desirable.

Although many methods for synthesizing isoquinoline analogues are known, classic methods such as the Pomeranz–Fritsch reaction have considerable drawbacks, including the use of strong acids and elevated temperatures,<sup>5</sup> which are not suitable for sensitive substrates. For that reason, not all functional and protecting groups are tolerated. In recent years, especially in the laboratories of Larock and co-workers, new transition-metal catalyzed reactions using phenyl acetylenes as starting materials have been developed for the synthesis of substituted isoquinolines (Scheme 1).<sup>6</sup> These reactions have proven to be extremely efficient in the synthesis of a wide variety of 3,4-substituted

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**Scheme 1.** Transition-Metal Catalyzed 3,4-Disubstituted Isoquinoline Synthesis**Scheme 2.** PtBr<sub>2</sub>-Catalyzed Isoquinoline Synthesis

isoquinolines and other carbo- and heterocycles.<sup>7</sup> It is, however, not possible to synthesize 1,3,4-trisubstituted isoquinolines by these methods.

During our research on the synthesis of functionalized indene derivatives with a platinum catalyst,<sup>8</sup> we observed in one case the formation of a 1,3-substituted isoquinoline (Scheme 2).<sup>9</sup> To date only aldimine-type substrates were known to undergo the transformation shown in Scheme 1, but the result shown in Scheme 2 suggests that proper choice of substrates and/or reagents may overcome that limitation to afford 1-substituted isoquinolines.

In our case, the two methyl substituents of the  $-NMe_2$  functional group act as the leaving group, formally eliminating ethane. Upon consideration of the pathway of the transformation, it occurred to us that azide ( $-N_3$ ), with nitrogen as the leaving group, instead of dimethylamine would be a far better nitrogen source of the isoquinoline framework. Furthermore, to gain access to 1,3,4-trisubstituted isoquinolines, we considered using an electrophile as the reaction mediator, since it would be incorporated into the final product. Iodonium is well-suited for this purpose, and hence, it offers clear and powerful potential for further assembly of molecular diversity at C4. It is well-known that coinage metals (Cu, Ag, Au)<sup>10</sup> and other related

**Table 1.** Iodine-Mediated Cyclization of 2-Alkynylbenzyl Azides **1**

entry	compd <b>1</b>	R	I <sup>+</sup>	base	yield (%) <sup>a</sup>	
					<b>2</b>	<b>3</b>
1	<b>1a</b>	Ph	I <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub>	95 <sup>b</sup>	—
2	<b>1b</b>	<i>p</i> -OMe-Ph	I <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub>	94 <sup>b</sup>	—
3	<b>1c</b>	<i>p</i> -CF <sub>3</sub> -Ph	I <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub>	95 <sup>b,c</sup>	—
4	<b>1d</b>	1-cyclohexenyl	I <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub>	82 <sup>b</sup>	—
5	<b>1e</b>	<i>tert</i> -butyl	I <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub>	71 (21d) <sup>b</sup>	—
6	<b>1f</b>	2-pyridinyl	I <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub>	—	86 <sup>b</sup>
7	<b>1g</b>	H	I <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub>	—	56 <sup>b,d</sup>
8	<b>1h</b>	Me	Py <sub>2</sub> IBF <sub>4</sub> <sup>e</sup> (NIS) <sup>f</sup>	— <sup>e</sup> (NaHCO <sub>3</sub> ) <sup>f</sup>	55 <sup>e</sup> (42) <sup>f</sup>	—
9	<b>1i</b>	<i>n</i> -butyl	Py <sub>2</sub> IBF <sub>4</sub> <sup>e</sup> (NIS) <sup>f</sup>	— <sup>e</sup> (NaHCO <sub>3</sub> ) <sup>f</sup>	67 <sup>e</sup> (66) <sup>f</sup>	—
10	<b>1j</b>	CH <sub>2</sub> TMS	Py <sub>2</sub> IBF <sub>4</sub> <sup>e</sup> (NIS) <sup>f</sup>	— <sup>e</sup> (NaHCO <sub>3</sub> ) <sup>f</sup>	69 <sup>e</sup> (62) <sup>f</sup>	—

<sup>a</sup> Isolated yield. <sup>b</sup> I<sub>2</sub> (5 equiv), K<sub>3</sub>PO<sub>4</sub> (5 equiv), CH<sub>2</sub>Cl<sub>2</sub> (0.1 M), rt, 24 h, Ar. <sup>c</sup> Reaction time 72 h. <sup>d</sup> The crystal structure is given in the Supporting Information for ref 7f. <sup>e</sup> Py<sub>2</sub>IBF<sub>4</sub> (2 equiv), HBF<sub>4</sub> in Et<sub>2</sub>O (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, −78 °C, 1 h, Ar. <sup>f</sup> NIS (5 equiv), NaHCO<sub>3</sub> (1 equiv), (CH<sub>2</sub>Cl)<sub>2</sub> (0.1 M), 50 °C, 72 h, Ar.

metals<sup>11</sup> exhibit strong Lewis acidity toward unsaturated C—C bonds ( $\pi$ -electrophilic nature) as well as toward lone pairs of electrons associated with heteroatoms ( $\sigma$ -electrophilic nature). Especially, gold-catalyzed reactions of alkynes are of keen interest in modern organic synthesis.<sup>10</sup> However, in the case of the gold-catalyzed reactions, gold is not incorporated into the final product, and a vinyl–gold intermediate that may be formed during the reaction is not easily trapped by an external nucleophile; therefore, further functionalization at C4 is not possible. It was expected that an iodo substituent would be introduced at C4 in the iodine-mediated reaction.

## Results and Discussion

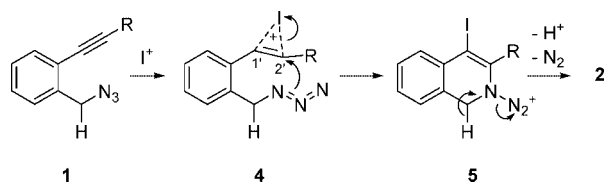
The initial cyclization study of **1a** using 5 equiv of iodine and 5 equiv of K<sub>3</sub>PO<sub>4</sub> as the base in CH<sub>2</sub>Cl<sub>2</sub> provided the desired isoquinoline **2a** in an excellent yield of 95% (Table 1, entry 1). Further optimization of the reaction conditions (e.g., smaller amounts of iodine, different bases such as Al<sub>2</sub>O<sub>3</sub> or NEt<sub>3</sub>, other solvents such as THF, or changes of temperature) failed to improve and in some cases even decreased the yield. Therefore, we continued to use the initially tested reaction conditions for the synthesis of 3,4-disubstituted isoquinolines.

For R = Ar (Table 1, entries 1–3), the cyclization of **1a–c** proceeded very smoothly to give the desired isoquinolines **2a–c** in yields of 94–95%, but in the case of **1c**, which bears an electron-withdrawing substituent, the reaction time had to be extended to 3 days to reach full conversion. Besides the aromatic substituents, the nonaromatic derivatives **1d** and **1e** (entries 4 and 5), bearing olefinic and sterically bulky *tert*-butyl substituents, respectively, were tolerated without problems as well, giving the desired products **2d** and **2e** in 82 and 71% yield, respectively. It must nevertheless be mentioned that for **1e**, the reaction time was extended to 21 days to reach almost full conversion. To our surprise, when R = 2-pyridinyl (**1f**) and H

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- (11) (a) For computations on  $\sigma$ - versus  $\pi$ -electrophilicity of various metal halides toward lone-pair  $\sigma$  electrons of carbonyl and imine groups and toward  $\pi$  electrons of unsaturated C—C bonds, see: Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817–7831. (b) Yamamoto, Y. *J. Org. Chem.* **2008**, *73*, 5210.

Scheme 3. Plausible Reaction Mechanism



(**1g**) were tested, instead of the expected isoquinolines, the corresponding bis(iodine) adducts **3f** and **3g** were obtained selectively in 86 and 56% yield, respectively (entries 6 and 7). The structure of **3g** was determined unambiguously by X-ray crystal structure analysis (see the Supporting Information for ref 7f). Attempts to convert **3f** and **3g** to the desired isoquinolines **2f** and **2g** by prolonged heating or abstraction of iodide by silver resulted only in decomposition of **3f** and **3g**. When small- or medium-sized aliphatic substituents such as Me, *n*-butyl, and CH<sub>2</sub>TMS (**1h–j**) were used, the desired cyclization products (**2h–j**) were obtained by the use of the Barluenga reagent or NIS (entries 8–10).

In view of these results, we assume the reaction mechanism to be working as shown in Scheme 3.<sup>12</sup> At first the electrophilic I<sup>+</sup> activates the alkyne via a cyclic iodonium ion, opening the way for the nucleophilic cyclization of the azide at C2' (**4**). When the intermediate **5** loses N<sub>2</sub> and H<sup>+</sup>, the isoquinoline **2** is formed. The proximity of the pyridinyl substituent to the reaction center enables the basic nitrogen atom to coordinate to the iodonium ion, thereby holding it close to C2' and preventing the azide from forming the new C2'–N bond. In the case of the smallest substituent, R = H, the cyclic iodonium ion **4** is twisted, strengthening the C2'–I bond and preventing closure of the nucleophilic ring. Therefore, the iodide anion in the solution has enough time to add at the cationic center at C1'.

To prevent the formation of the bis(iodine) adduct **3**, iodonium sources with less nucleophilic counterions were tested. While ICl led to a mixture of iodine- and chloride-substituted isoquinolines and NBS gave no conversion, the Barluenga reagent (Py<sub>2</sub>IBF<sub>4</sub>/HBF<sub>4</sub>) in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C for 1 h and NIS in (CH<sub>2</sub>Cl)<sub>2</sub> at 50 °C for 72 h gave the desired isoquinolines **2h–j** without formation of the bis(iodine) adducts (entries 8–10). The Barluenga reagent afforded the products **2h–j** in 55, 67, and 69% yield, while NIS gave the products in 42, 66, and 62% yield, respectively.

Of course, we were more interested in the synthesis of even more highly substituted isoquinolines; therefore, we used **1k** as a model substrate to optimize the synthesis of 1,3,4-substituted isoquinolines. To our surprise, we had to change the base from K<sub>3</sub>PO<sub>4</sub> (used for the reactions in Table 1) to NaHCO<sub>3</sub> to achieve the best results, isolating the desired product **2k** in 69% yield (Table 2, entry 1). As we could prove, the substituents R<sup>1</sup>–R<sup>4</sup> had only a very small influence on the yield of the products. Irrespective of whether electron-rich, electron-deficient, or electron-neutral substituents on the benzene ring were used, the yields of the highly substituted products **2k–u** were in general between 60–70%. The reactions of **1l** and **1m** having aliphatic substituents at R<sup>1</sup> proceeded without problems and gave yields of 73 and 68%, respectively (entries 2 and 3). It should be noted that it was even possible to form the tricyclic product **2m** in 68% yield (entry 3).

Table 2. Iodine-Mediated Synthesis of Highly Substituted Isoquinolines

1k-w							2k-w	
entry	compd 1	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	I <sup>+</sup>	yield of <b>2</b> (%) <sup>a</sup>
1	<b>1k</b>	Me	H	H	H	H	I <sub>2</sub> <sup>b</sup>	69
2	<b>1l</b>	<i>n</i> -hexyl	H	H	H	H	I <sub>2</sub> <sup>b</sup>	73
3	<b>1m</b>	–(CH <sub>2</sub> ) <sub>3</sub> –	H	H	H	H	I <sub>2</sub> <sup>b</sup>	68
4	<b>1n</b>	Ph	H	H	H	H	I <sub>2</sub> <sup>b</sup>	68 <sup>c</sup>
5	<b>1o</b>	CH <sub>2</sub> OAc	H	H	H	H	Py <sub>2</sub> IBF <sub>4</sub> <sup>d</sup>	61
6	<b>1p</b>	Me	H	–O–CH <sub>2</sub> –O–	H	H	I <sub>2</sub> <sup>b</sup>	58
7	<b>1q</b>	cyclopropyl	H	–O–CH <sub>2</sub> –O–	H	H	I <sub>2</sub> <sup>b</sup>	62
8	<b>1r</b>	Bn	H	–O–CH <sub>2</sub> –O–	H	H	I <sub>2</sub> <sup>b</sup>	59
9	<b>1s</b>	isobutyl	H	–O–CH <sub>2</sub> –O–	H	H	I <sub>2</sub> <sup>b</sup>	66
10	<b>1t</b>	Me	H	H	NO <sub>2</sub>	H	I <sub>2</sub> <sup>b</sup>	58
11	<b>1u</b>	cyclopropyl	H	H	NO <sub>2</sub>	H	I <sub>2</sub> <sup>b</sup>	72
12	<b>1v</b>	Me	H	OMe	OMe	OMe	I <sub>2</sub> <sup>b</sup>	0
13	<b>1w</b>	Me	H	H	–CH=CH–CH=CH–	H	I <sub>2</sub> <sup>b</sup>	0

<sup>a</sup> Isolated yield. <sup>b</sup> I<sub>2</sub> (5 equiv), NaHCO<sub>3</sub> (1 equiv), CH<sub>2</sub>Cl<sub>2</sub> (0.1 M), rt, 24 h, Ar. <sup>c</sup> Two side products were formed that could not be separated out; the yield of **2n** was determined by NMR. <sup>d</sup> Py<sub>2</sub>IBF<sub>4</sub> (2 equiv), HBF<sub>4</sub> in Et<sub>2</sub>O (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 1 h, Ar.

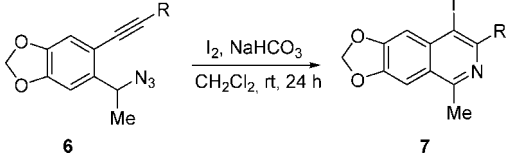
However, problems were encountered with substrates **1n** and **1o**. In the case of the phenyl-substituted substrate **1n** (entry 4), two unidentified side products were formed that could not be separated from the desired product. Thus, the yield of 68% for the desired product **2n** itself was not an isolated yield but was determined by NMR analysis of the mixture. In the other problematic case, substrate **1o** was not stable toward basic reaction conditions, and therefore, it was treated with the acidic Barluenga reagent, forming the product **2o** in 61% yield (entry 5). The Barluenga reagent was also tested for entries 3 and 7, and we obtained the desired products in yields similar to those achieved using I<sub>2</sub>. In general, a rather large excess of I<sub>2</sub> (5 equiv) was used in the cyclization; if we used 2 equiv of I<sub>2</sub> in the reaction of **1k**, it took 3 days to complete the reaction. Use of 5 equiv of I<sub>2</sub> was required in order to enhance the reaction speed.

For the substrates **1p–u** having either electron-rich or electron-deficient substituents on the benzene ring, we also tested further substituents for R<sup>1</sup> and found that in each case we were able to form the desired product with a yield between 60 and 70% (entries 6–11). A general rule, it was not possible to determine which substituent for R<sup>1</sup> is more favored. It seems that all substituents at R<sup>1</sup> are equally tolerated, making this new methodology very useful for further application. Unfortunately, we did find some limitations with respect to substitution at the C5 position of the aromatic ring (**1v** and **1w**): substituents other than R<sup>5</sup> = H were not tolerated (entries 12–13). It is most probably the case that as a result of steric hindrance between the substituent R<sup>5</sup> and the iodonium ion of intermediate **4**, C2' is turned away from the azide. This prevents the closure of the nucleophilic ring by the azide at C2' that is necessary to form the isoquinoline ring. For that reason, the products **2v** and **2w** were not formed.

While we could show that the substituents R<sup>1</sup>–R<sup>4</sup> had only a small influence on the outcome of the reaction, we found that in the case of the 3,4-di-RO substituents on the aromatic ring (**1p**, **6a**, and **6b**), the electronic properties of the phenyl

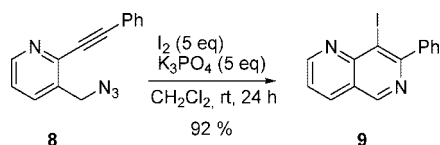
(12) A similar reaction pathway as described takes place; see: Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261.



**Table 3.** Influence of the Phenyl Substituent of the R Group


entry	starting material	R	product, yield (%) <sup>a,b</sup>
1	<b>1p</b>	Ph	<b>2p</b> , 58
2	<b>6a</b>	<i>p</i> -tolyl	<b>7a</b> , 93
3	<b>6b</b>	<i>p</i> -COOEt-Ph	<b>7b</b> , 11

<sup>a</sup> Isolated yield. <sup>b</sup> I<sub>2</sub> (5 equiv), NaHCO<sub>3</sub> (1 equiv), CH<sub>2</sub>Cl<sub>2</sub> (0.1 M), rt, 24 h, Ar.

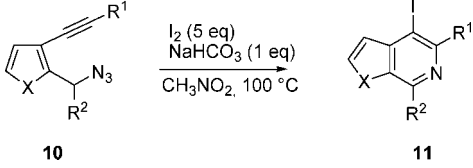
**Scheme 4.** Synthesis of 7,8-Substituted 1,6-Naphthylpyridine

substituents at the alkyne terminus (R) exerted a strong influence on the yields of the isoquinolines (Table 3).

While the substrate **1p** gave the isoquinoline **2p** in 58% yield (see Table 2, entry 6), the yield of the isoquinoline **7a** increased dramatically to 93% when the electron-rich substrate **6a** was used (Table 3, entry 2). This is the best yield among all of the reactions examined by the present methodologies. In contrast, when **6b** with the  $\pi$ -electron-withdrawing ester was tested, the yield of the product **7b** dropped to only 11%. This indicates that while the substituents R<sup>1</sup>–R<sup>4</sup> at the benzylic and aromatic positions can be chosen without restrictions, only the substituent R at the alkyne seems to be important for the outcome of the reaction. It should be noted that in the case of the simple substrate **1c** that has R<sup>1</sup>–R<sup>4</sup> = H and only a  $\sigma$ -electron-withdrawing *p*-Ph–CF<sub>3</sub> group at the alkynyl terminus, the electronic property of R did not exert any influence on the product yield (Table 1, entries 1–3, **1a**–**c**). Its only effect is to significantly increase the reaction time required for complete conversion. We therefore attribute the high yield of product **2c** to the better stability of substrate **1c** under the reaction conditions applied.

Besides substituted isoquinolines, we were extremely interested in the synthesis of substituted bicyclic heteropyridine derivatives, which might show interesting biological properties (Scheme 4). As expected, unlike the substrate **1f**, where the nitrogen of pyridine was incorporated into the alkynyl terminus R, the substrate **8** was smoothly converted into 1,6-naphthylpyridine **9** in 92% yield without formation of the bis(iodine) adduct. Perhaps the coordination of the nitrogen of the pyridine ring of **8** to the iodonium ion of **4** facilitates the attack of the azide nitrogen at the C2' cationic center.

Nevertheless, additional optimizations of the reaction conditions were necessary when the five-membered heterocyclic derivatives **10** were used instead of the phenyl substrates **1**. The use of the original standard reaction conditions optimized for **1** resulted in only minor formation of the desired products **11**, but we soon found that this problem could be overcome through the use of CH<sub>3</sub>NO<sub>2</sub> at 100 °C instead of CH<sub>2</sub>Cl<sub>2</sub> at room temperature (Table 4). In the above experiments (Tables 1–3), we have known that the most favored combination of the substituents is Ph as R<sup>1</sup> and H as R<sup>2</sup>. Actually, the pyrrole substrate **10a** gave the desired product **11a** in 72% yield in less

**Table 4.** Iodine-Mediated Cyclization of Five-Membered Heterocyclic Derivatives


entry	compd 10	X	R <sup>1</sup>	R <sup>2</sup>	time (h)	yield of 11 (%) <sup>a,b</sup>
1	<b>10a</b>	N–Ts	Ph	H	2.5	72
2	<b>10b</b>	N–Ts	Ph	<i>n</i> -hexyl	1	77
3	<b>10c</b>	N–Ts	<i>n</i> -butyl	H	3	25
4	<b>10d</b>	O	Ph	H	18	61
5	<b>10e</b>	S	Ph	H	24	71
6	<b>10f</b>	S	Ph	Me	1.5	26
7	<b>10g</b>	S	<i>n</i> -butyl	H	5.5	46

<sup>a</sup> Isolated yield. <sup>b</sup> I<sub>2</sub> (5 equiv), NaHCO<sub>3</sub> (1 equiv), CH<sub>3</sub>NO<sub>2</sub>, 100 °C.

than 2.5 h. The thiophene substrate **10e** worked equally well, forming the product **11e** in 71% yield within 24 h. The furan substrate **10d** was also able to form the isoquinoline ring, but only in 61% yield after 18 h. Different results were obtained when we used an alkyl substituent for R<sup>2</sup>. While the pyrrole **10b** (entry 2) exhibited even better performance than the parent compound **10a**, forming the desired product **11b** in 77% yield in less than 1 h, the thiophene analogue **10f** gave **11f** only in an unacceptable yield of 26% (entry 6). Relatively small alkyl substituents at R<sup>1</sup> were not tolerated: both **10c** and **10g** (entries 3 and 7) gave low yields (25 and 46%, respectively).

To prove that our new method can be successfully applied to the synthesis of more complicated substrates, we chose as the target molecule norchelerythrine **12**, which exhibits potent pharmacological activities such as antitumor and antiviral activities (Scheme 5).<sup>13</sup>

The retrosynthetic analysis of **12** is shown in Scheme 5. At first, we break ring C between C11 and C11'. This gives us the 3,4-disubstituted isoquinoline **13**, which most probably can be synthesized through our new method. The key azide substrate therefore has to be the diaryl acetylene **14**, which can be derived from the commercially available benzaldehydes **15** and **16**.

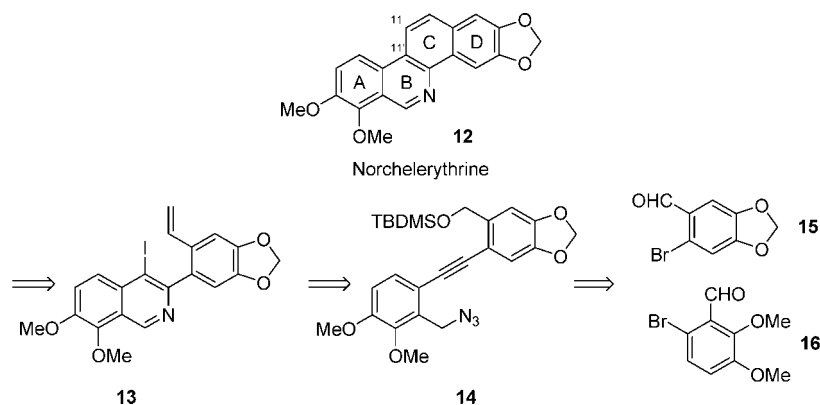
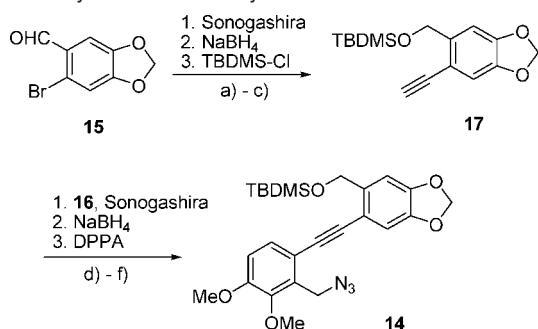
Compound **17**, which had been prepared previously,<sup>14</sup> was synthesized via Sonogashira coupling between 6-bromopiperonal **15** and TMS–acetylene with a yield of 69% (Scheme 6) followed by reduction of the aldehyde and deprotection of the acetylene in one step using NaBH<sub>4</sub> in MeOH. Protection of the resulting benzyl alcohol with TBDMSCl gave **17** in a very high yield. Sonogashira coupling between **17** and **16** gave the corresponding diaryl acetylene in 81% yield. The reduction of the aldehyde with NaBH<sub>4</sub> in MeOH/THF gave the benzyl alcohol in 94% yield, and this was followed by the formation of key substrate **14** in 91% yield using DPPA. Accordingly, **14** was synthesized from **15** in six steps in a total yield of 44%. In addition, no purification by chromatography was necessary to this point because all of the products could be purified by crystallization.

The key reaction from **14** to the 3,4-disubstituted isoquinoline **18** proceeded perfectly smoothly under the previously optimized

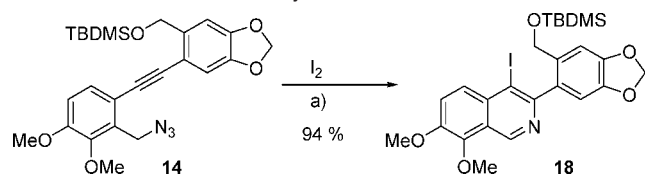
(13) (a) Chen, J.-J.; Fang, H.-Y.; Duh, C.-Y.; Chen, I.-S. *Planta Med.* **2005**, *5*, 470–475. (b) For a recent synthesis of norchelerythrine, see: Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. I* **2001**, 523–528.

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## Scheme 5. Retrosynthetic Analysis of Norchelerythrine 12

Scheme 6. Synthesis of the Key Intermediate 14<sup>a</sup>

<sup>a</sup> (a) **15**, TMS–acetylene (1.3 equiv), PdCl<sub>2</sub> (2.5 mol %), PPh<sub>3</sub> (5 mol %), CuCl (3.6 mol %), NEt<sub>3</sub> (3 equiv), CH<sub>3</sub>CN, Δ, 16 h, 69%; (b) NaBH<sub>4</sub> (0.75 equiv), MeOH, 0 °C, 3 days, 92%; (c) TBDMS-Cl (1.3 equiv), imidazole (1.8 equiv), THF, 0 °C, 99%; (d) **16** (0.85 equiv), PdCl<sub>2</sub> (5 mol %), PPh<sub>3</sub> (10 mol %), NEt<sub>3</sub> (3 equiv), CH<sub>3</sub>CN, Δ, 16 h, 81%; (e) NaBH<sub>4</sub> (0.85 equiv), MeOH/THF (1:1.25), 0 °C, 3 h, 94%; (f) (PhO)<sub>2</sub>PON<sub>3</sub> (1.25 equiv), DBU (1.35 equiv), toluene, 16 h, 91%.

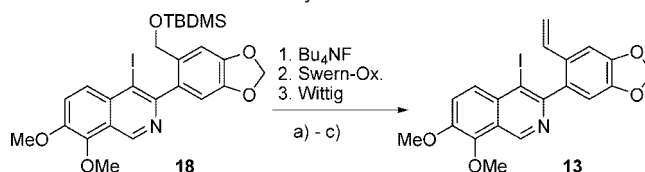
Scheme 7. Iodine-Mediated Cyclization of 14<sup>a</sup>

<sup>a</sup> (a) I<sub>2</sub> (5 equiv), K<sub>3</sub>PO<sub>4</sub> (5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 24 h, 94%.

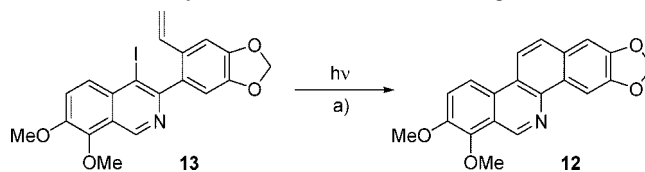
reaction conditions without further modifications, giving the desired product **18** in an almost quantitative yield of 94% (Scheme 7).

To conclude the synthesis of the natural product, all that was left was the formation of the last ring C. First, the TBDMS group of **18** was deprotected with Bu<sub>4</sub>NF, forming the free benzyl alcohol in 92% yield (Scheme 8). Afterward, the only problematic step was encountered. Surprisingly, after oxidation of the alcohol, the resulting benzaldehyde proved to be highly unstable, giving black tar upon standing. After many trials, we found that the problem could be avoided by use of the following procedure: the unstable benzaldehyde obtained through Swern oxidation was purified only by a quick aqueous workup and immediately added to a Wittig ylide solution (10 equiv) to form the stable styrene derivative **13** in 87% yield over two steps (Scheme 8).

To conclude the synthesis of **12**, we examined Heck-type cyclizations of **13** for many trials, but only the corresponding 5-exo-product **24** was obtained. After many attempts, we finally

Scheme 8. Formation of the Styrene Derivative 13<sup>a</sup>

<sup>a</sup> (a) Bu<sub>4</sub>NF·3H<sub>2</sub>O (1.5 equiv), THF, 0.5 h, 92%; (b) DMSO (4 equiv), (COCl)<sub>2</sub> (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, −78 °C, followed by benzyl alcohol, 0.5 h, NEt<sub>3</sub> (3 equiv), 1 h, aqueous workup only (!); (c) the benzaldehyde was immediately taken up in THF and added to a Wittig solution [PPh<sub>3</sub>CH<sub>3</sub>Br (10 equiv), KO<sup>t</sup>Bu (10 equiv), THF], 0 °C, 14 h, dark, 87% over two steps.

Scheme 9. Photocyclization of 13 To Form the Ring C of 12<sup>a</sup>

<sup>a</sup> (a) hν, NEt<sub>3</sub> (2 equiv), CHCl<sub>3</sub>, 24 h, 57%.

considered using a light-induced radical cyclization/elimination to form ring C (Scheme 9). We expected this to be possible given the special instability of iodine compounds toward light. To our surprise, we found no previous report of a similar reaction using iodine as a light-sensitive group for the formation of a phenyl ring. One report about the formation of a heterocycle using a similar approach was later found.<sup>15</sup>

To test our photocyclization idea, we irradiated **13** in an NMR tube in CDCl<sub>3</sub>. The NMR spectra taken after 8 h showed only the desired natural product **12** without any of the styrene derivative **13**.<sup>16</sup> Under optimized conditions with 2 equiv of NEt<sub>3</sub>, we isolated a 10:1 mixture of the products 6-endo **12** and 5-exo **24** (see the Supporting Information), with an isolated yield of 57% for the desired natural product **12**; the two regioisomeric products **12** and **24** could be separated by a column chromatography. Therefore, we not only successfully applied the newly developed method to form the highly substituted isoquinoline **12** but also found a new way to form a phenyl ring from the iodoarylstyrene under mild conditions using the unique properties of the light-sensitive iodine moiety.

In conclusion, we have presented a general and flexible approach to highly substituted isoquinoline building blocks, which can then be further functionalized. Depending on the

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requirements of the substrates employed, acidic, basic, or neutral reaction conditions can be used, making this method compatible with labile and highly functionalized molecules. Because the reaction conditions are mild, a wide variety of substituents are tolerated. The free choice of substituents along the benzyl area and the possible application to the five-membered heteroaromatic substrates especially make this method useful for further use in the synthesis of small molecules, natural product synthesis, and technical applications.

### Experimental Section

Azide **1k** (7.22 mg, 0.29  $\mu$ mol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (0.1 M), and  $\text{NaHCO}_3$  (1 equiv) was added. Iodine (5 equiv) was added, and the solution was stirred in the dark for 24 h. After complete conversion, as tested by TLC, the reaction was quenched with  $\text{Na}_2\text{S}_2\text{O}_3$  solution. The product was extracted with ethyl acetate, dried over  $\text{MgSO}_4$ , and purified by column chromatography ( $\text{SiO}_2$ ) to yield 6.9 mg of **2k** (69%).

Barluenga reagent ( $\text{Py}_2\text{IBF}_4$ ) (2 equiv) under argon was dissolved in  $\text{CH}_2\text{Cl}_2$  (0.16 M) and cooled to  $-78^\circ\text{C}$ , and  $\text{HBF}_4$  (54% in  $\text{Et}_2\text{O}$ ) (2 equiv) was added. The solution was transferred to azide **1o** (25 mg, 82  $\mu$ mol) dissolved in  $\text{CH}_2\text{Cl}_2$  (1.33 M) at  $-78^\circ\text{C}$ . After 1 h, the reaction was quenched with  $\text{Na}_2\text{S}_2\text{O}_3$  solution. The product was extracted with ethyl acetate, dried over  $\text{MgSO}_4$ , and purified by column chromatography ( $\text{SiO}_2$ ) to yield 20.1 mg of **2o** (61%).

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

JA805326F

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