



HAL
open science

Straightforward Access to 2-Iodoindolizines via Iodine-Mediated Cyclization of 2-Pyridylallenes

Thibaut Martinez, Ismail Alahyen, Gilles Lemière, Virginie Mouriès-Mansuy,
Louis Fensterbank

► **To cite this version:**

Thibaut Martinez, Ismail Alahyen, Gilles Lemière, Virginie Mouriès-Mansuy, Louis Fensterbank. Straightforward Access to 2-Iodoindolizines via Iodine-Mediated Cyclization of 2-Pyridylallenes. *Organic Process Research and Development*, 2020, 24 (5), pp.817-821. 10.1021/acs.oprd.9b00418 . hal-03082062

HAL Id: hal-03082062

<https://hal.science/hal-03082062>

Submitted on 18 Dec 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Straightforward Access to 2-Iodoindolizines via Iodine-Mediated Cyclization of 2-Pyridylallenes

Thibaut Martinez, Ismail Alahyen, Gilles Lemière*, Virginie Mouriès-Mansuy* and Louis Fensterbank*

Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, 75005 Paris, France

Supporting Information Placeholder

ABSTRACT: A metal-free access to 2-iodo-1,3-disubstituted indolizines has been developed. The proposed synthesis is relatively simple and efficient and involves the iodine-triggered 5-*endo-trig* cyclization of 2-pyridylallene precursors. While it can be conducted on a gram scale, the preparation of the precursors is straightforward and does not always require intermediate purifications. The obtained 2-iodoindolizines can be further functionalized through cross coupling reactions.

Keywords: allenes, indolizines, iodine, cyclization, pyridine

INTRODUCTION

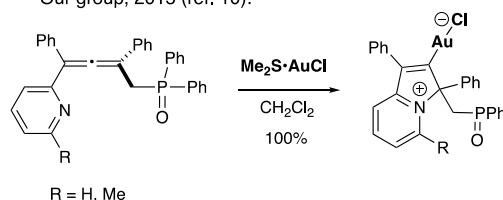
Indolizines are key motifs in organic chemistry present in a myriad of biologically active compounds¹ and used as precursors of valuable organic materials.² In the latter case, tuning of the properties can be achieved via variation of the substituents of the two rings. Logically, this has elicited a strong attention in developing new synthetic pathways to these compounds. Originally synthesized by Scholtz³ and Chichibabin⁴ at the beginning of the XXth century through condensation reactions, new methods, essentially dipolar cycloaddition and cycloisomerization reactions have been developed since then, giving access to a plethora of polysubstituted indolizine rings⁵ as well as indolizines bearing a halogen at position 2.⁶ Although there is a growing interest in accessing 1,2,3-trisubstituted indolizines,⁷ to the best of our knowledge, only Kim and coll. have proposed a method to synthesize 1,3-disubstituted 2-iodoindolizines from propargylic acetates.^{8,9} The position 2 being iodinated, it should allow post-functionalization through commonly used transition metal cross-coupling reactions or a radical pathway. Also, a brief literature survey shows that pyridylallenes are valuable intermediates for the synthesis of indolizines via 5-*endo-trig* cyclisation reaction under electrophilic activation.^{10,11}

In 2015, our group has reported on the cyclization of 2-pyridylallenes using dimethyl sulfide gold (I) chloride as π -Lewis acid to provide a new family of gold complexes (Scheme 1).¹² Also relevant to our project, Michelet and Toullec described in 2016 the synthesis of 2-iodoindenes by activation of arylallenes using *N*-iodosuccinimide (NIS) as iodonium source.¹³ We surmised that if the cyclization of 2-pyridylallenes can also be triggered by such electrophiles, the resulting indoliziniums could evolve towards the formation of 2-iodo-1,3-disubstituted indolizines after elimination of one of the groups present on the newly formed quaternary carbon center (Scheme 1).

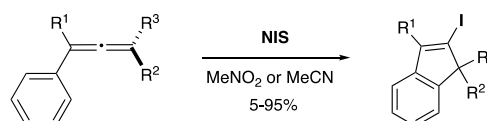
Scheme 1. Electrophile-induced cyclization reactions of arylallenes

• Previous works :

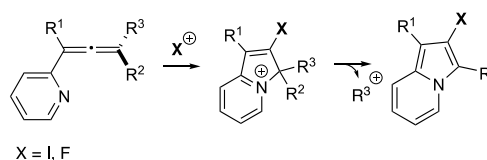
Our group, 2015 (ref. 10):



Michelet and Toullec, 2016 (ref. 11):



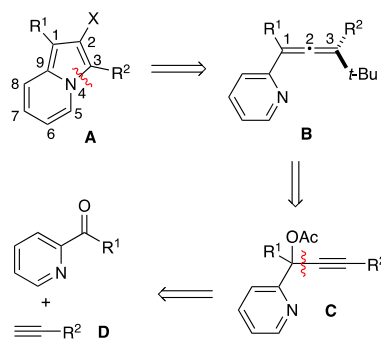
• This work:



RESULT AND DISCUSSION

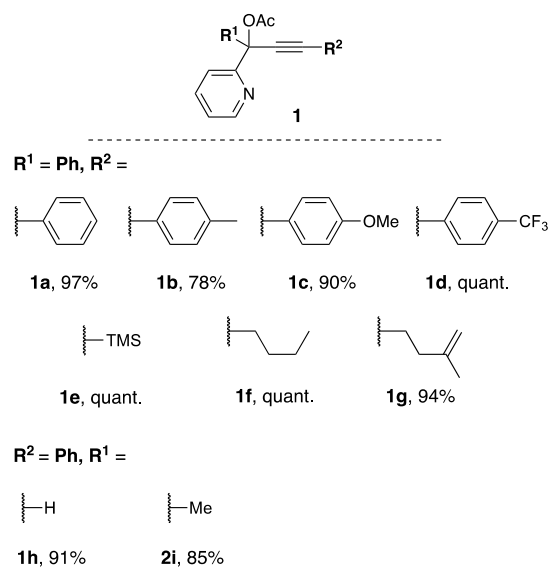
The retrosynthetic analysis led us to consider the C3-N4 disconnection: we reasoned that the key cyclization/elimination sequence of **B** would provide indolizine **A** (Scheme 2). The required tetrasubstituted allenic precursors **B** of indolizines **A** would be readily accessed from propargylic acetate **C** via S_N2' type reaction. The latter can be obtained through a 1,2-addition/acetylation sequence from 2-pyridyl ketone and alkyne derivatives **D**.

Scheme 2. Retrosynthetic analysis for the synthesis of 1,2,3-trisubstituted indolizines



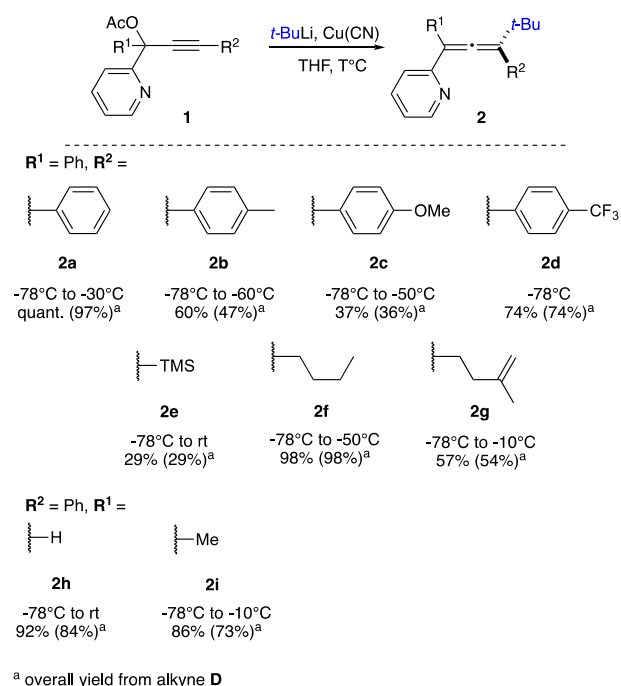
Following this strategy, nine propargylic acetates were obtained (**1a-i**) in high yields over two steps (Scheme 3).

Scheme 3. Synthesis of propargylic acetates 1



Propargylic acetates **1** were then converted into tetrasubstituted allenes **2** bearing a *tert*-butyl group at the C3 position using the *tert*-butylcyanocuprate reagent following Krause's procedure¹⁴ (Scheme 4). This reaction quickly showed high efficiency on propargylic acetate **1a** since a quantitative yield was observed for the formation of **2a**. It was then extended to the other propargylic acetates **1b-i** to obtain the corresponding seven tetrasubstituted allenes **2a-i** even when R¹ are a hydrogen or a methyl instead of a phenyl group. We found out that the temperature needed to be carefully controlled to obtain the desired products. While **2f**, **2h** and **2i** were obtained in excellent yield, the reaction showed less efficiency on other substrates, especially from **1d** and **1e**. Moreover, each of these allenes and intermediates were found to be perfectly stable under bench conditions and no purification was required until the final allene compound was obtained.

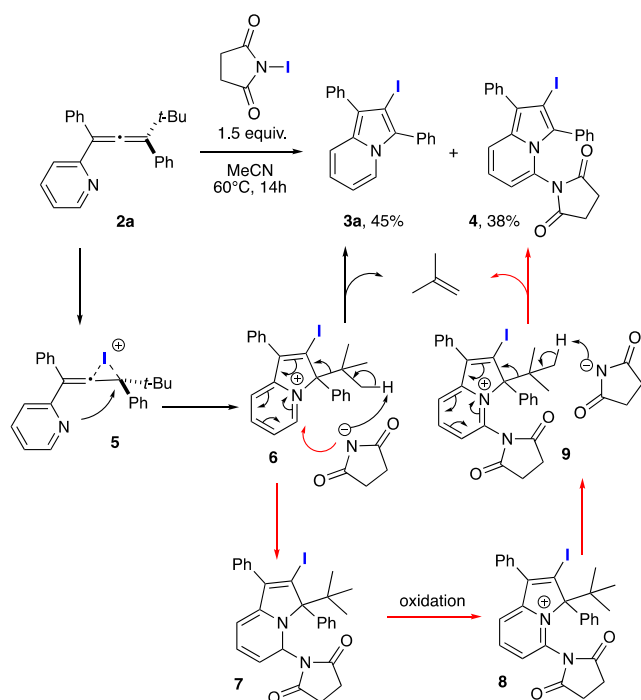
Scheme 4. Synthesis of 2-pyridylallenes 2



^a overall yield from alkyne **D**

Next, we investigated the cyclisation reaction, starting initially with NIS as an electrophilic iodine source. When conducted at room temperature, a significant quantity of starting material remained untouched after two hours with no evolution of the reaction. Increasing the temperature to 60°C led to the full conversion of 2-pyridylallene **2a** to afford the desired 2-iodoindolizine **3a** along with the succinimide adduct **4**. Iodoindolizine **3a** results as expected from the loss of the *tert*-butyl group on the cyclic indolizinium intermediate **6** (Scheme 5), itself originating from the cyclization of iodonium **5**. The formation of **4** could be rationalized by considering the *N*-addition of the succinimide on the activated α position of the iodypyridinium **6** to give adduct **7**. The latter would rearomatize after oxidation to **8**¹⁵ and α -adduct **4** is generated *via* **9**. Another pathway transiting via an iodypyridinium, generated by iodination of the pyridine nitrogen, and α -addition was discarded since model 2-vinylpyridine remained intact in the reaction conditions. This suggests that the preliminary activation of the allene as in **5** is required for the addition of the succinimide.¹⁶ The formation of **3a** validated our strategy and we then pursued on the optimization of the reaction conditions in order to suppress the formation of the undesired product **4**.

Scheme 5. Cyclization of 2a using NIS



When 1.2 equivalents of iodine were employed as the electrophilic halogen source instead of NIS (Table 1), 43% yield of 2-iodoindolizine **3a** was obtained along with the 1,3-disubstituted indolizine **10** in a 80/20 ratio (Table 1, entry 1). This latter compound is suspected to originate from the cyclization reaction of 2-pyridylallene **2a** promoted by hydroiodic acid generated *in situ* after the cyclization/elimination process. Interestingly, **3a** was formed in greater proportion by decreasing the temperature to 60°C (entry 2). Using two equivalents of iodine and setting the temperature to 70°C proved to be beneficial since **3a** was obtained in 84% with only traces of indolizine **10** (entry 3). Running the reaction in basic conditions using potassium carbonate as an acid scavenger allowed to avoid totally the formation of the undesired product **10** and afforded **3a** in excellent yield (entry 4). This reaction turned out to be very convenient from a practical point of view since it could be run on the gram scale (see Scheme 6) and pure material was recovered from the simple filtration of the greenish solid formed while the excess of iodine was neutralized. Moreover, the structure of 2-iodoindolizine **3a** was unambiguously confirmed by X-ray diffraction (Figure 1).¹⁷

Table 1. Conditions optimization for the iodocyclization

Entry	T°C	I ₂	K ₂ CO ₃	Yield of 3a ^a	Yield of 10 ^a
1	80°C	1,2 equiv.	-	43% ^a	18% ^a

2	60°C	1,2 equiv.	-	48% ^a	12% ^a
3	70°C	2 equiv.	-	84%	Traces
4	70°C	2 equiv.	2 equiv.	92%	-

^a yields calculated from a mixture of **3a/10**.

We then extended this iodocyclization reaction to other 2-pyridylallenes using the optimized conditions (Scheme 6). 3-aryloindolizines **3b**, **3c** and **3i** were obtained very efficiently from **2b**, **2c** and **2i**, respectively, while the yield was slightly lower from electrodeficient aromatic ring **2d** bearing a trifluoromethyl group. Alkylindolizines **3f** and **3g** were also obtained albeit with moderate yield, maybe due to a lower stabilization of the cationic charge that is developing on **5**. Also with precursors bearing an alkyl chain (**2f** and **2g**), we suspect that decumulation of the allene takes place. We could show that the cyclization process was not restricted to substrates bearing a phenyl group at the allenic position (R¹) with engaging trisubstituted allene **1h** and methylated derivative **1i**. While the expected 2-iodoindolizine **3h** was obtained in a good yield (78%) accompanied by a side product (see SI), the introduction of a methyl at that position proved very rewarding since **3i** was obtained in quantitative yield. We also reasoned that a TMS group could be a better leaving group than the *tert*-butyl group. Gratifyingly, when TMS-substituted 2-pyridylallene **2e** was used as substrate, *tert*-butyl substituted 2-iodoindolizine **3e** was selectively obtained in satisfactory yield (74%).

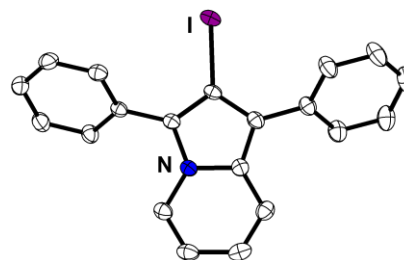
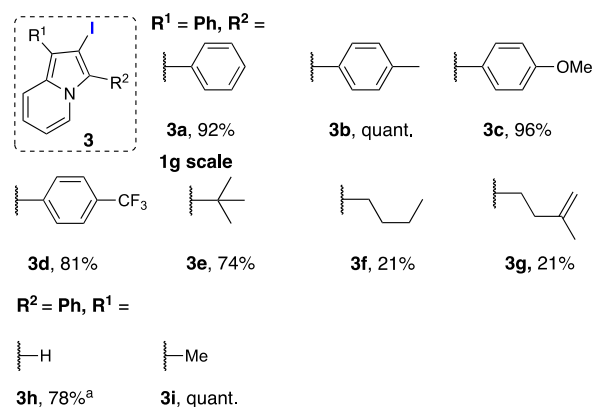


Figure 1. Crystal structure of compound **3a** (H atoms are omitted for clarity).

Scheme 6. Synthesis of 2-iodoindolizines

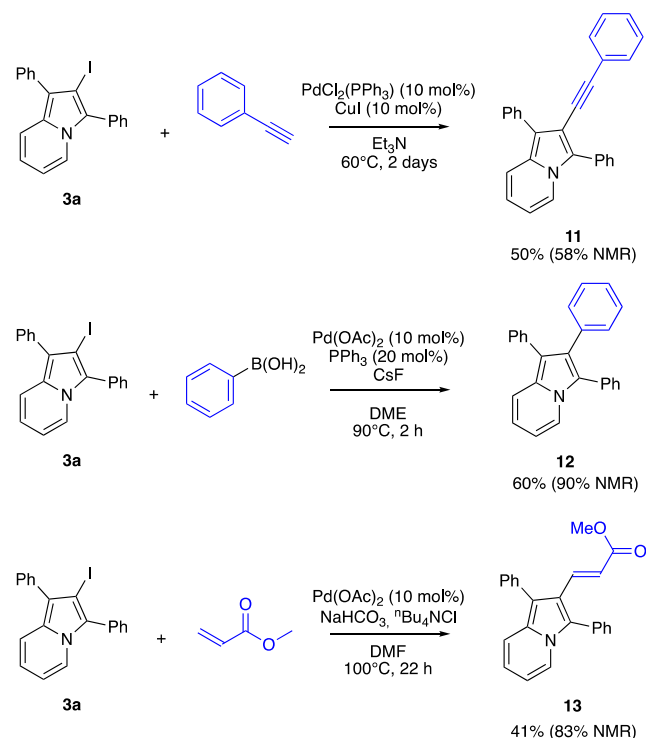


^a: 1.05 equiv. of I₂ was used and a second product was obtained (see SI)

This reaction gives access to 1,2,3-trisubstituted indolizines bearing an iodine atom at position 2 which can then be functionalized.

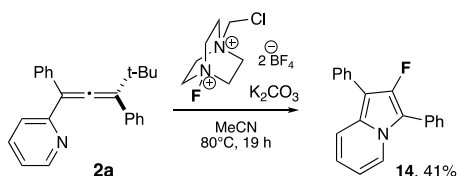
Inspired by the work of Kim,⁸ we investigated further functionalization with widely employed pallado-catalyzed cross coupling reactions such as Sonogashira, Suzuki and Heck reactions using **3a** as model substrate (Scheme 7). The Sonogashira cross coupling was conducted with phenylacetylene to yield 1,2,3-trisubstituted indolizine **11** in moderate yield. Compound **12** and **13** were synthesized using a Suzuki and a Heck coupling with phenylboronic acid and methylacrylate, respectively. NMR yields for those two coupling reactions were excellent while isolated yield turned out to be lower than expected due to possible degradation during purification which was not optimized.

Scheme 7. Palladium-catalyzed cross-coupling reactions of 2-iodoindolizines



Furthermore, since fluorinated aromatic compounds show interesting properties in medicinal chemistry¹⁸ we extended the reaction using Selectfluor as an electrophilic fluorine source. In that case, the 2-fluoroindolizine **14** was obtained.

Scheme 8. Synthesis of 2-fluoroindolizine



In summary, we propose a new pathway to access highly functionalized indolizines *via* a 5-*endo-trig* cyclisation of 2-pyridylallene precursors. An example of this cyclization was conducted on the gram scale with high efficiency and convenient purification procedure. The presence of the iodo group at the

position 2 allows for late 2-functionalization steps which have been barely described in the literature. Three common transition metal-catalyzed cross-coupling reactions were given as examples but the iodo group should be useful for other types of 2-substitution. An example of activation of a 2-pyridylallene with electrophilic fluorine to deliver a 2-fluoroindolizine was also performed. As an extension of this work, different azacyclic allene cyclisations using various electrophiles are currently underway and should allow access to other unprecedented indolizine type scaffolds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data for all new compounds, ¹H, ¹³C and ¹⁹F NMR spectra.

AUTHOR INFORMATION

Corresponding Author

gilles.lemiere@sorbonne-universite.fr;
virginie.mansuy@sorbonne-universite.fr; [lou-
is.fensterbank@sorbonne-universite.fr](mailto:louis.fensterbank@sorbonne-universite.fr)

Author Contributions

TM did some experimental work and contributed to the writing of the article. IA did some experimental work. GL, VMM and LF designed the reactions and wrote the article.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The authors are grateful to Sorbonne Université (PhD grant to TM) and CNRS for funding of this work. They also thank Geofrey Gontard for the XRD analysis of **3a**.

REFERENCES

- (1) (a) Sharma, V.; Kumar, V. Indolizine: A Biologically Active Moiety. *Med. Chem. Res.* **2014**, *23*, 3593–3606. (b) Singh, G. S.; Mmatli, E. E. Recent Progress in Synthesis and Bioactivity Studies of Indolizines. *Eur. J. Med. Chem.* **2011**, *46*, 5237–5257.
- (2) Huckaba, A. J.; Giordano, F.; McNamara, L. E.; Dreux, K. M.; Hammer, N. I.; Tschumper, G. S.; Zakeeruddin, S. M.; Grätzel, M.; Nazeeruddin, M. K.; Delcamp, J. H. Indolizine-Based Donors as Organic Sensitizer Components for Dye-Sensitized Solar Cells. *Adv. Energy Mater.* **2015**, *5*, 1401629.
- (3) Scholtz, M. Die Einwirkung von Essigsäureanhydrid Auf A-Picolin. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 734–746.
- (4) Tschitschibabin, A. E. Tautomerie in Der Pyridin-Reihe. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1607–1617.
- (5) Sadowski, B.; Klajn, J.; Gryko, D. T. Recent Advances in the Synthesis of Indolizines and Their π -Expanded Analogues. *Org. Biomol. Chem.* **2016**, *14*, 7804–7828.

- (6) For some recent syntheses of 2-haloindolizines, see: (a) via orthometallation: Amaral, M. F. Z. J.; Baumgartner, A. A.; Vescechi, R.; Clososki, G.C. Directed Metalation of 1-Ester Substituted Indolizines: Base/Electrophile-Controlled Regioselective Functionalization *Org. Lett.* **2015**, *17*, 238–241. (b) via [3+3] annulation: Park, S.; Kim, I. Electron-withdrawing group effect in aryl group of allyl bromides for the successful synthesis of indolizines via a novel [3+3] annulation approach *Tetrahedron* **2015**, *71*, 1982–1991. (c) via a brominated pyrrole: Kodet, J. G.; Wiemer, D. F. Synthesis of Indole Analogues of the Natural Schweinfurthins *J. Org. Chem.* **2013**, *78*, 9291–9302.
- (7) (a) Wang, X.; Li, S. Y.; Pan, Y. M.; Wang, H. S.; Liang, H.; Chen, Z. F.; Qin, X. H. Samarium(III)-Catalyzed C(Sp³)-H Bond Activation: Synthesis of Indolizines via C-C and C-N Coupling between 2-Alkylazaarenes and Propargylic Alcohols. *Org. Lett.* **2014**, *16*, 580–583. (b) Chai, W.; Kwok, A.; Wong, V.; Carruthers, N. I.; Wu, J. A Practical Parallel Synthesis of 2-Substituted Indolizines. *Synlett* **2003**, *2003*, 2086–2088. (c) Tan, X. C.; Liang, Y.; Bao, F. P.; Wang, H. S.; Pan, Y. M. Silver-Mediated C-H Bond Functionalization: One-Pot to Construct Substituted Indolizines from 2-Alkylazaarenes with Alkynes. *Tetrahedron* **2014**, *70*, 6717–6722. (d) Kucukdisli, M.; Opatz, T. A Modular Synthesis of Polysubstituted Indolizines. *Eur. J. Org. Chem.* **2012**, *2012*, 4555–4564. (e) Li, F.; Chen, J.; Hou, Y.; Li, Y.; Wu, X. Y.; Tong, X. 1,3-Dipolar Cycloadditions of 4-Acetoxy Allenates: Access to 2,3-Dihydropyrazoles, 2,3-Dihydroisoxazoles, and Indolizines. *Org. Lett.* **2015**, *17*, 5376–5379. (f) Brioché, J.; Meyer, C.; Cossy, J. Synthesis of 2-Aminoindolizines by 1,3-Dipolar Cycloaddition of Pyridinium Ylides with Electron-Deficient Ynamides. *Org. Lett.* **2015**, *17*, 2800–2803. (g) Chernyak, D.; Skontos, C.; Gevorgyan, V. Two-Component Approach toward a Fully Substituted N-Fused Pyrrole Ring. *Org. Lett.* **2010**, *12*, 3242–3245. (h) Li, Z.; Chernyak, D.; Gevorgyan, V. Palladium-Catalyzed Carbonylative Cyclization/Arylation Cascade for 2-Aroylindolizine Synthesis. *Org. Lett.* **2012**, *14*, 6056–6059. (i) Xu, T.; Alper, H. Synthesis of Indolizine Derivatives by Pd-Catalyzed Oxidative Carbonylation. *Org. Lett.* **2015**, *17*, 4526–4529. (j) Kim, I.; Won, H. K.; Choi, J.; Lee, G. H. A Novel and Efficient Approach to Highly Substituted Indolizines via 5-Endo-Trig Iodocyclization. *Tetrahedron* **2007**, *63*, 12954–12960.
- (8) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. Expedient Synthesis of Indolizine Derivatives via Iodine Mediated 5-Endo-Dig Cyclization. *Tetrahedron Lett.* **2007**, *48*, 6863–6867.
- (9) For an extension of this work, see also: (a) Choi, J.; Ge, H. L.; Kim, I. Efficient Synthesis of Highly Substituted Indolizines via Iodocyclization and 1,2-Shift. *Synlett* **2008**, 1243–1249. (b) Heller, S. T.; Kiho, T.; Narayan, A. R. H.; Sarpong, R. Protic-Solvent-Mediated Cycloisomerization of Quinoline and Isoquinoline Propargylic Alcohols: Syntheses of (±)-3-Demethoxyerythridinone and (±)-Cocculidine. *Angew. Chem. Int. Ed.* **2013**, *52*, 11129–11133. (c) Makarov, A. S.; Uchuskin, M. G.; Hashmi, A. S. K. Intramolecular Azavinyl Carbene-Triggered Rearrangement of Furans *Chem. Sci.* **2019**, DOI 10.1039/c9sc02299f.
- (10) (a) Ma, S. Electrophilic Addition and Cyclization Reactions of Allenes *Acc. Chem. Res.* **2009**, *42*, 1679–1688. (b) Canaque, T.; Truscott, F. M.; Rodriguez, R.; Maestri, G.; Malacria, M. Electrophilic Activation of Allenes and Allenynes: Analogies and Differences between Bronsted and Lewis Acid Activation *Chem. Soc. Rev.* **2014**, *43*, 2916–2926.
- (11) (a) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. Highly Efficient Synthesis of Functionalized Indolizines and Indolizinones by Copper-Catalyzed Cycloisomerizations of Propargylic Pyridines. *J. Org. Chem.* **2007**, *72*, 7783–7786. (b) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. Multisubstituted N-Fused Heterocycles via Transition Metal-Catalyzed Cycloisomerization Protocols. *Tetrahedron* **2008**, *64*, 6876–6883. (c) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. A Novel Cu-Assisted Cycloisomerization of Alkynyl Imines: Efficient Synthesis of Pyrroles and Pyrrole-Containing Heterocycles. *J. Am. Chem. Soc.* **2001**, *123*, 2074–2075. (d) Chernyak, D.; Gadamsetty, S. B.; Gevorgyan, V. Low Temperature Organocopper-Mediated Two-Component Cross Coupling/Cycloisomerization Approach toward N-Fused Heterocycles. *Org. Lett.* **2008**, *10*, 2307–2310. (e) Chernyak, D.; Gevorgyan, V. Organocopper-Mediated Two-Component SN^{2'}-Substitution Cascade towards N-Fused Heterocycles. *Chem. Heterocycl. Compd.* **2012**, *47*, 1516–1526. (f) Zhang, L.; Li, X.; Liu, Y.; Zhang, D. Palladium-Catalyzed Highly Efficient Synthesis of Functionalized Indolizines via Cross-Coupling/Cycloisomerization Cascade. *Chem. Commun.* **2015**, *51*, 6633–6636. (g) For a review, see: Wang, L.-X.; Tang, Y.-L. Cycloisomerization of Pyridine-Substituted Propargylic Alcohols or Esters to Construct Indolizines and Indolizinones. *Eur. J. Org. Chem.* **2017**, 2207–2213.
- (12) Vanitcha, A.; Gontard, G.; Vanthuyne, N.; Derat, E.; Mouriès-Mansuy, V.; Fensterbank, L. Synthesis of Allenes Bearing Phosphine Oxide Groups and Investigation of Their Reactivity toward Gold Complexes. *Adv. Synth. Catal.* **2015**, *357*, 2213–2218.
- (13) Grandclaudon, C.; Michelet, V.; Toullec, P. Y. Synthesis of Polysubstituted 2-Iodoindenes via Iodinium-Induced Cyclization of Aryllallenes. *Org. Lett.* **2016**, *18*, 676–679.
- (14) (a) Jansen, A.; Krause, N. Transition Metal-Promoted Synthesis of Functionalized and Unfunctionalized Pyridylallenes. *Synthesis (Stuttg.)* **2002**, *14*, 1987–1992. (b) Jansen, A.; Krause, N. Exceptional Reactivity and Selectivity of Lower-Order Cyanocuprates in the SN^{2'}-Substitution of Propargyl Acetates. *Inorganica Chim. Acta* **2006**, *359*, 1761–1766. (c) Löhr, S.; Averbeck, J.; Schürmann, M.; Krause, N. Synthesis and Complexation Properties of Allenic Bipyridines, a New Class of Axially Chiral Ligands for Transition Metal Catalysis. *Eur. J. Inorg. Chem.* **2008**, 552–556.
- (15) For some oxidations of dihydropyridines, (a) with DDQ, see: Gerasuto, A. I.; Hsung, R. P. An Intramolecular aza-[3+3] Annulation Approach to Azaphenylene Alkaloids. Total Synthesis of Myrrhine *J. Org. Chem.* **2007**, *72*, 5934–5946. (b) with Br₂ or NBS, see: Parenty, A. D.; Smith, L. V.; Pickering, A. L.; Long, D.-L.; Cronin, L. General One-Pot, Three-Step Methodology Leading to an Extended Class of N-Heterocyclic Cations: Spontaneous Nucleophilic Addition, Cyclization and Hydride Loss *J. Org. Chem.* **2004**, *69*, 5934–5946.
- (16) The introduction of a succinimidyl group at the 2-position has been reported from pyridine oxides, see: Zucker, S.A.; Wossidlo, F.; Weber, M.; Lentz, D.; Tzschucke, Palladium-Catalyzed Directed Halogenation of Bipyridine N-Oxides *J. Org. Chem.* **2017**, *82*, 5616–5635. We thank one referee for bringing this paper to our attention and for helpful remarks.
- (17) The structure was deposited at the Cambridge Crystallographic Data Centre with number CCDC 1955817 and can be obtained free of charge via www.ccdc.cam.ac.uk.
- (18) (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. (b) Purser, S.; Moore, R. P.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (c) Wang, J.; Sanchez-Rosello, M.; Acena, J.-L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001 - 2011) *Chem. Rev.* **2014**, *114*, 2432–2506.