

Indium(III) Catalyzed Reactions of Vinyl Azides and Indoles

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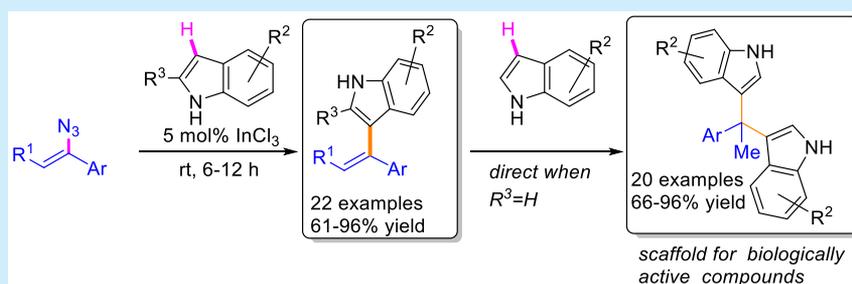
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ABSTRACT: Indium trichloride catalyzes the reaction of vinyl azides with unfunctionalized indoles to give vinyl indoles. This is the first example of displacement of the azide group by a carbon nucleophile while preserving the vinyl function. The protocol employs very mild reaction conditions and offers excellent yields of diverse 3-vinyl indoles. It is amenable to gram scale. Access to a library of 3,3'-bis(indolyl)methanes through condensation of vinyl azides with 2 equiv of an indole is demonstrated.

Vinyl azides are chemical chameleons. The unique properties of the azide function renders vinyl azides able to serve as a source of electrons for reaction with an electrophile¹ or a radical² as well as able to let nitrogen serve as a leaving group in reactions with a nucleophile^{1e,3} (Scheme 1a).⁴ This first step typically leads to different imine type species that may undergo further reactions.⁴ Thus, the first step in the chemistry of vinyl azides is typically at the α -position of the azide moiety.⁴ In addition, vinyl azides have a rich chemistry in cycloaddition reactions and are able to form nitrenes and azirines.⁴ The recent upsurge in studies on vinyl azides is probably due to their ready availability in high yields from feedstock alkenes^{2b,5} and alkynes.⁶

Surprisingly, substitution of the azide group on the sp^2 carbon with preservation of the alkene system (Scheme 1b) is unknown yet would be an attractive type of reactivity and open up many new possibilities in chemistry. Combined with the multitude of methods for alkene functionalization,⁷ such a reaction would not only provide a metaphorical novel color to the vinyl azide chameleonic properties, but also allow novel access to functionality of value in, e.g., materials and medicinal chemistry. We proposed attaining this goal using catalysis. In such a process, it would of course be necessary to reversibly attach an electrophilic catalyst, e.g., a Lewis acid, exemplified in Scheme 1b by indium trichloride (2), at the α -position of vinyl azide 1, giving rise to an electrophilic diazo-imine species 3 (Scheme 1b). Attack at the α -position is dictated by the reactivity of vinyl azides with electrophiles.^{1,4}

This initial step would allow a nucleophile such as, e.g., indole 4 to attack at the azide bearing carbon in 3 with formation of 5. E2 type elimination of indium-trichloride and

azide anion 7 would lead to formation of the charged species 6 and close the catalytic cycle. This step would likely be irreversible.

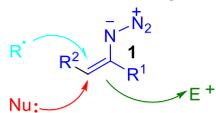
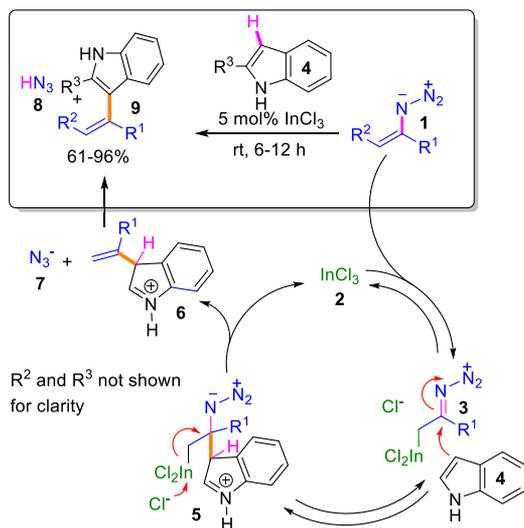
Finally, azide anion would abstract a proton from 6 to give the product vinyl indole 9 and hydrazoic acid 8. Formally this would constitute a substitution reaction on a vinyl (sp^2) carbon with azide as the leaving group. In contrast to reactions with other electrophiles, the reaction would be driven by an electrophilic catalyst, thereby uniquely preserving the double bond.

Challenging this proposal was that Brønsted acid activation of vinyl azides has been shown by Hassner et al.⁸ to lead predominantly to Schmidt type 1,2-rearrangements to furnish amides, or hydrolysis to give ketones in the presence of water. Chiba and co-workers⁹ and Bi et al.¹⁰ have shown the same to occur using superstoichiometric amounts of boron-trifluoride etherate or substoichiometric Tf_2NH ¹¹ and elegantly trapped the intermediates with different electrophiles. These reactions possibly take place through intermediates like 3 (with a proton or boron in lieu of Indium).⁸⁻¹¹ Notably, an intermediate, analogous to 3, in Scheme 1b has been proposed in a mechanistic study on the $InBr_3$ catalyzed reaction of enol ethers with silyl ketene imines.¹²

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Scheme 1. This Work in Perspective and Mechanistic Hypothesis

a) Known chameleon reactivity of vinyl azides at the α -positionb) This work: Lewis acid catalyzed C(sp²)-N₃/C(sp²)-H coupling with formal substitution of the azide

As outlined in Scheme 1b, we pursued proof of concept in the form of a direct C(sp²)-C(sp²) bond forming reaction between vinyl azides with indoles to give vinyl indoles. To the best of our knowledge, there are no examples of such a transformation. Vinyl indoles are attractive intermediates for the synthesis of alkaloids. Previously vinyl indoles have been prepared from nitrimines and indoles.¹³ However, nitrimines are not attractive starting materials as their preparation is very low yielding (nitrimines were prepared in 12–42% yield, but typically yields were less than 20%).¹³ Vinyl indoles have also been prepared from ketones, but the conditions require strong acid and high temperature, incompatible with many functionalities.¹⁴

In order to identify an effective Lewis acid catalyst, (1-azidovinyl)benzene **10** and 2-methyl-1*H*-indole **11** were selected as suitable reactants for optimizing the reaction conditions (Table 1). As expected, treatment of the 1:1 mixture of **10** and **11** with the Lewis acid BF₃·OEt₂ (Table 1, entry 2) or a Brønsted acid (stoichiometric HCl formed *in situ* from acetyl chloride and methanol, Table 1, entry 1) at 0 °C to room temperature does not afford the desired 3-vinyl-indoles **12**. However, acetophenone can be observed by TLC and isolated after water workup.^{8a}

A number of metal salt Lewis acids such as zinc(II) triflate, copper(II) triflate, as well as magnesium(II) triflate and calcium(II) triflate also fail to give any desired product (Table 1, entries 3–6). In contrast, even substoichiometric (10 mol %) amounts of B(C₆F₅)₃ leads to formation of vinyl indole product **12** in 84% isolated yield (entry 7). The use of lanthanide Lewis acids was also investigated. Scandium(III) triflate catalyzes the reaction, but the reaction only reaches 70% conversion after 24 h (entry 8). In dichloroethane, the reaction is even slower (entry 10). At an increased temperature of 60 °C, scandium(III) triflate catalyzes the reaction to 100%

Table 1. Optimization of Reaction Conditions^a

entry	Lewis acid	mol % acid	T/°C	t/h	conv (%) ^b	yield (%) ^c
1	AcCl/MeOH	150	0	6	100	N.D. ^{d,e}
2	BF ₃ ·OEt ₂	100	rt	6	100	N.D. ^d
3	Zn(OTf) ₂	5	rt	24	100	N.D. ^d
4	Cu(OTf) ₂	5	rt	24	0	N.D.
5	Mg(OTf) ₂	5	rt	24	0	N.D.
6	Ca(OTf) ₂	5	rt	24	0	N.D.
7	B(C ₆ F ₅) ₃	10	rt	3	100	84
8	Sc(OTf) ₃	5	rt	24	70	66
9	Sc(OTf) ₃	5	60	24	100	78 ^f
10	Sc(OTf) ₃	5	rt	24	50	43
11	In(OTf) ₃	5	rt	8	100	89
12	InCl ₃	5	rt	6	100	96

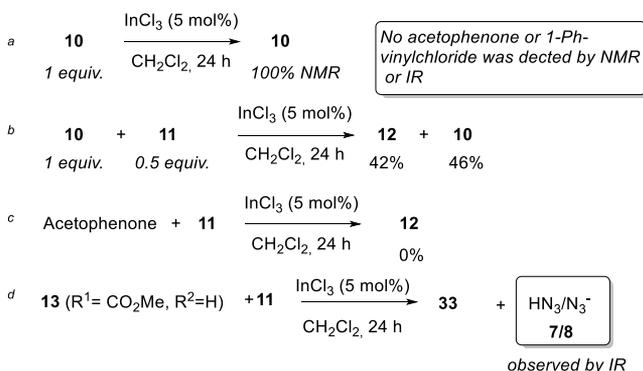
^aUnless otherwise specified, all reactions were performed with 1.0 mmol of **10**, 1.0 mmol of **11**, and CH₂Cl₂ as the solvent in 4–5 mL. See the Supporting Information for details. N.D. indicates that **12** was not detected. ^bConversion of **10**. ^cIsolated yields of **12**. ^dAcetophenone was formed. ^eSolvent was THF (2 mL). ^fSolvent was dichloroethane

conversion within 24 h (entry 9), but the yield is inferior to that of B(C₆F₅)₃ (entry 7). Remarkably, indium(III) triflate affords 89% yield of **12** in only 8 h (entry 11). Finally, the best result is achieved by carrying the reaction out in the presence of 5 mol % InCl₃ in CH₂Cl₂ at room temperature. Under these conditions, complete conversion is achieved in 6 h to give the 3-vinyl indole **12** as a single regioisomer in 96% isolated yield (Table 1, entry 12).

It was important to investigate whether the reaction proceeds via hydrolysis of the (1-azidovinyl)benzene (**10**) to the acetophenone observed in the early experiments (Table 1, entries 1–3). Accordingly, a series of reactions of **10** with varying stoichiometry of 2-methyl indole (**11**) were carried out, and the reactions were monitored. Reaction in the complete absence of **11** also affords no product, and the vinyl azide **10** is recovered unchanged (Scheme 2a). Neither acetophenone nor 1-phenyl-vinyl chloride was observed by IR or NMR of the reaction mixture. Thus, the observed acetophenone (Table 1, entries 1–3) is likely formed upon addition of water at the end of the reaction. When the reaction is carried out with 0.5 equiv of **11**, the product **12** is isolated in 42% yield along with unreacted **10** (46%, Scheme 2b). Again, no acetophenone is detected. Notably, acetophenone fails to react with indole **10** under the standard reaction conditions (Scheme 2c) and no product is observed. This makes the possibility of the mechanism going through a ketone as an intermediate highly unlikely.¹⁴ Additionally, signals attributable to azide are observed by IR spectroscopy in the reaction mixture after completion (see Supporting Information). These experiments support the mechanism outlined in Scheme 1b.

The reaction is readily scaled to gram scale. Thus, reaction of (1-azidovinyl)benzene gives **12** in 96% yield at 100 mg scale and a similar 91% yield at 2 g scale (Scheme 3). The scope of the reaction is fairly wide (Scheme 3). Reaction of (1-azidovinyl)benzene **13** (R¹ = H) with 2-phenyl-indole leads to

Scheme 2. Control Experiments



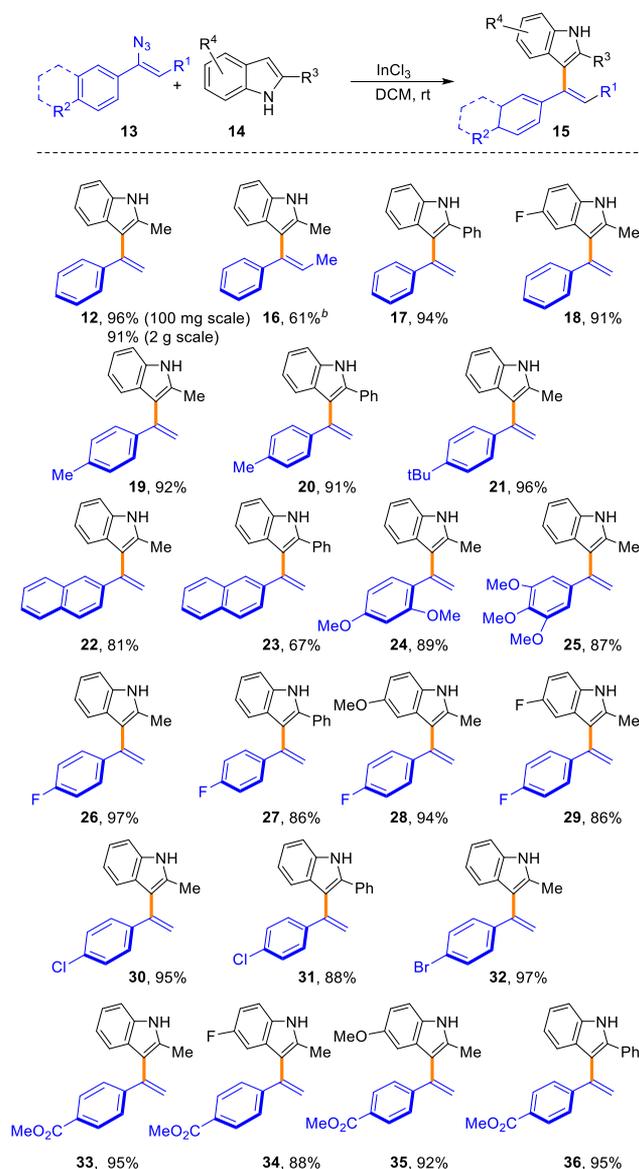
^aNo reaction observed in the absence of indole. ^bConversion is function of equivalents of indole. ^cAcetophenone is not an intermediate. ^dAzide signal does not fade during the reaction (see IR in the Supporting Information; see structure 33 in Scheme 3).

compound 17 in 94% yield. This indicates a low steric and electronic influence with regard to the 2-substituent on the indole. A *para*-methyl or even *tert*-butyl group on the 1-phenyl-vinyl-1-azide is also well tolerated (see compounds 19–21 in Scheme 3). These results similarly confirm the low importance of the nature of the 2-indole substituent. A naphthyl-substituent as the aromatic group of the vinyl azide 13 is also well tolerated (22 and 23 in Scheme 3).

The substitution pattern on the vinyl azide has a significant influence on reaction rate albeit not on the yield. Both 1-phenyl-vinyl azides with two or even three methoxy groups on the phenyl ring work well in the reaction giving products 24 and 25 in 89% and 87% yield, respectively, in only 12 h. Thus, the effect of an *ortho* substituent as is present in 1-(1-azidovinyl)-2,4-dimethoxybenzene used to prepare 24 does not appear to make any significant difference in the yield or rate. Vinyl azides with electron withdrawing substituents such as 12 ($R^1 = H, R^2 = F, Cl, \text{ or } Br$) give the products 26–32 in similar yields, but at a lower rate (Scheme 3). Methyl 4-(1-azidovinyl)benzoate 12 ($R^1 = H, R^2 = -CO_2Me$) reacts even slower with a variety of indoles to give products 33–36 in 88% to 95% yield over 18 h. Importantly, the reaction is not limited to terminal vinyl azides. While (*Z*)-(1-azidoprop-1-en-1-yl)benzene 13 ($R^1 = Me$) reacts sluggishly at room temperature, at 65 °C complete conversion is achieved in 18 h to give 16 in 61% isolated yield.

Due to the importance of fluorinated compounds in pharma,¹⁵ we also investigated the applicability of the reaction to fluorinated indoles and vinyl azides. Accordingly, reaction of 5-fluoro substituted 2-methyl-indole with (1-azidovinyl)benzene (10) gives product 18 in 91% yield, while reaction with methyl 4-(1-azidovinyl)benzoate (12, $R^1 = H, R^2 = -CO_2Me$) gives product 34 in 88% yield. Reaction of 1-(1-azidovinyl)-4-fluorobenzene (12, $R^1 = H, R^2 = F$) with 2-methyl-indole, 2-phenyl-indole, 5-methoxy-2-methyl-indole, and 5-fluoro-2-methyl-indole gives product 26 in 97% yield, 27 in 86% yield, 28 in 92% yield, and 29 in 86% yield. This showcases the applicability of the method to make fluorinated products and also the negligible influence of electron-donating and electron-withdrawing groups on the indole for the reaction outcome.

Interestingly, a C(2)-substituent on the indole is necessary if the vinyl-indole is the desired product. When the reaction of

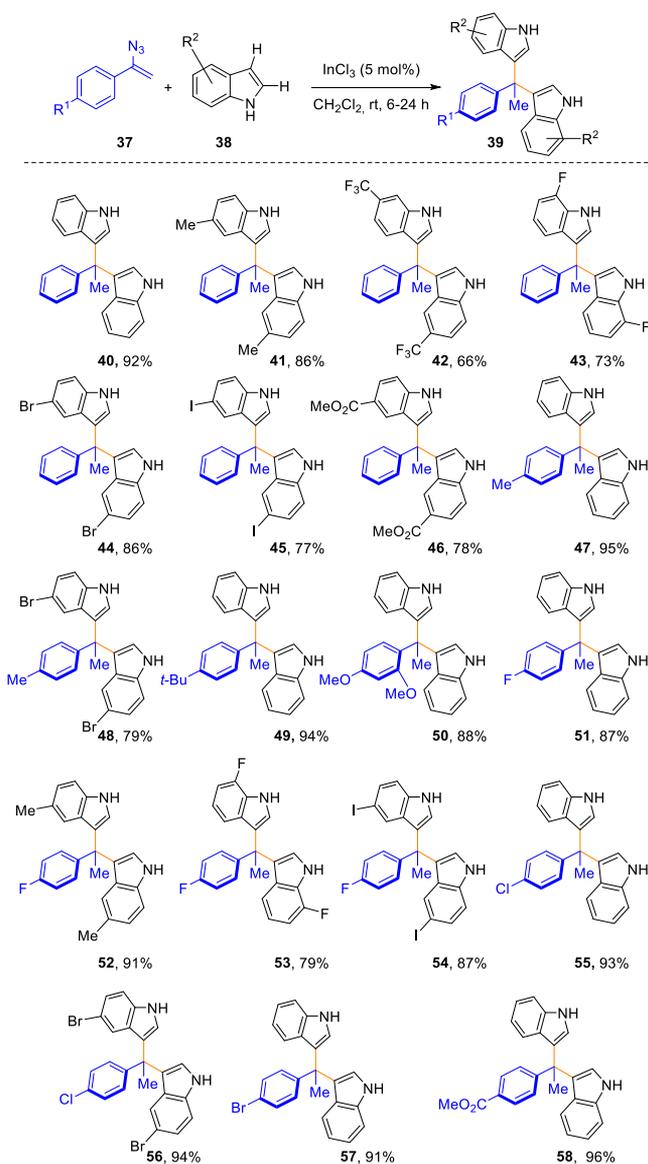
Scheme 3. Scope of the 3-Vinyl Indole Synthesis from Indoles and Vinyl Azides^a

^aUnless otherwise specified, all reactions were performed at room temperature. Yields are unoptimized isolated yields after flash chromatography. ^bReaction was conducted at 65 °C

(1-azidovinyl)benzene (37, $R^1 = H$) is carried out using 1 equiv of simple, i.e. 2,3-unsubstituted, indole, the bis(indolyl)methane 40 is formed as the only observable product together with unreacted starting material. When the amount of indole is increased to 2 equiv the product 40 is formed in 92% isolated yield. (Scheme 4). Clearly the initially formed vinyl-indole is so reactive it rapidly reacts a second time. This is likely due to the steric requirements of a 2-substitution forcing the indole to adopt a conformation with no coplanarity with the vinyl system (as drawn in Scheme 3). This would reduce the ability of the indole substituent to stabilize carbocationic species. In the absence of a 2-substituent, however, such stabilization is lower in energy, allowing these vinyl indoles to react faster under acidic conditions.

Indeed, slow addition of indole or performing the reaction at 0 or -15 °C does not lead to isolation of the vinyl indole but

Scheme 4. Scope of the Synthesis of Bis(indolyl) Methanes Synthesis from Indoles and Vinyl Azide^a



^aYields are unoptimized isolated yields after flash chromatography

always leads to the bis(indolyl)-methane product. Rather than perceiving this as a limitation, we saw this as an opportunity to prepare 3,3'-bis(indolyl)methanes (BIMs) in a single synthetic step (Scheme 4). BIMs are known to have various medicinal properties and are a common structure found in natural products and compounds with pharmaceutical properties.^{16,17}

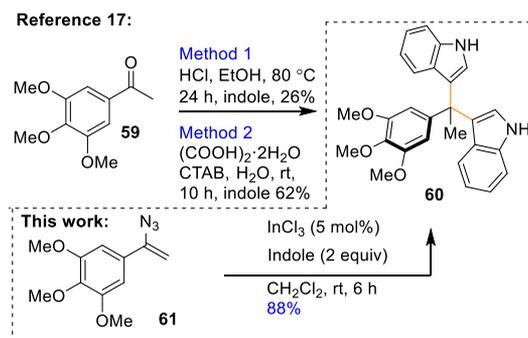
The scope of this reaction is quite wide. Similar to what was found in the synthesis of vinyl indoles, a wide range of substituents may be present in both the vinyl azide 37 and the indole 38 (Scheme 4). In the vinyl azide, both electron donating groups such as methyl, *tert*-butyl, and methoxy may be present on the phenyl group. Thus, BIMs 40–50 are all produced and isolated in yields ranging from 66% to 94% yield. Again an *ortho* substituent on the vinyl azide seems to have little effect, and product 50 is formed 88% isolated yield within only 8 h. A fluorine, chlorine, or bromine substituent on the phenyl of 37 leads to products 51–57 that are isolated in 79–94% yield. A ester functionalized vinyl azide 37 ($\text{R}^1 = \text{CO}_2\text{Me}$)

reacts with indole to give 58 in 96% yield. As already observed, electron-withdrawing groups somewhat retard the rate.

With respect to the indole, alkyl, methoxy, ester, and halide substituents are all tolerated. Interestingly both fluorine in indole and the vinyl azide may be present. See, e.g., compound 53 which is isolated in 79% yield (Scheme 4). Fluorine may also be present as a CF_3 group as may be seen for product 42 which was isolated in 66% yield (Scheme 4). In products 45 and 54, an iodine is present, and in 44, 56, and 57 a bromide is present (Scheme 4). Bromide is also found in vinyl indole 32 (Scheme 3). These functionalities are completely compatible with the reaction conditions and may be used as a handle for classical transition metal catalyzed coupling chemistry. These reactions (Schemes 3 and 4) are therefore completely orthogonal to classical coupling reactions.

To further demonstrate the utility of the BIM preparation method, we prepared the synthesis of bis(indolyl)methane 60, a molecule that inhibits growth and induces apoptosis in human prostate cancer cells (Scheme 5).¹⁷ Mariangela et al.

Scheme 5. Synthesis of Apoptosis Agonist Bis(indolyl)methane 60



reported the synthesis of compound 60 using condensation of indole with 3,4,5-trimethoxyacetophenone (59) in the presence of catalytic amounts of hydrochloric acid as well as by a second method involving the use of oxalic acid and *N*-cetyl-*N,N,N*-trimethylammonium bromide in water in moderate yields (26% and 62%, respectively).¹⁷ For comparison, reaction of vinyl azide 61 and indole (2 equiv) afforded the desired BIM 60 in a single step in 88% yield (Scheme 5).

In conclusion, indium trichloride acts as a catalyst that brings about formal substitution of the azide by a carbon nucleophile. This is in contrast to the classical reactivity of vinyl azides that usually react at the α -position. Proof of concept has been achieved in the form of a $\text{C}(\text{sp}^2)\text{-N}_3/\text{C}(\text{sp}^2)\text{-H}$ cross coupling reaction of vinyl azides with indoles. The method offers excellent yields of structurally diverse 3-vinyl indoles. The vinyl azide starting materials are readily available from alkenes or alkynes. Additionally, the reaction has been extended to direct formation of bis(indolyl)methanes with potential pharmaceutical importance. Further application of this concept and its scope will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c00919>.

Procedures, characterization data, and spectroscopic studies of the reaction and the resulting data (PDF)

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Author Contributions

The manuscript was written through contributions of both authors.

Notes

The authors declare no competing financial interest.

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