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Allenyl Azide Cycloaddition Chemistry. Photochemical Initiation and CuI Mediation Leads to Improved Regioselectivity

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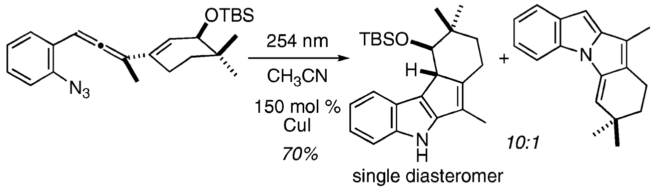
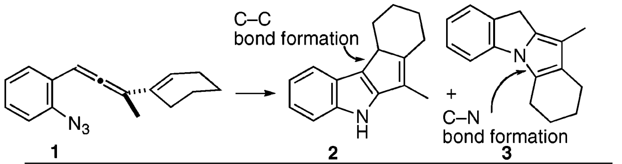
ABSTRACT



Irradiation of 2-(3-alkenyl)allenylphenyl azides in the presence of excess CuI furnished functionalized 2,3-cyclopentenylindoles in good yield with only trace amounts of competitive C–N-bonded regioisomeric products. These results represent a significant departure from the modest-to-nonexistent regioselectivity that attended thermal cyclization of these allenyl azide substrates.

The synthesis of annelated indoles from thermolysis of 2-allenylphenyl azides was described recently, Scheme 1, entry a.[1] This cascade reaction sequence displayed little regioselectivity during the terminal bond formation, and both C−C- and C−N-bonded products were observed in roughly equal proportions. An ongoing interest in the total synthesis of indole-terpene-derived alkaloids exemplified by, inter alia, the fisherindoles,[2] yuehchukene,[3] and the nodulisporanes[4] would be advanced if selectivity for the C−C-bonded isomer could be increased. As detailed below, new studies have revealed that the combination of photochemical initiation and CuI together provide this enhanced regioselectivity, with exclusive formation of the C(2)−C(3) annelated indole product analogous to **2** in the most favorable cases.

Scheme 1. Initial Photochemical and Thermal Results



		2	3
		yield (%, chrom. isolated)	
entry *a*	110 °C, toluene	36	51
entry *b*	254 nm, CH_3CN	32	27

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[1] Feldman, K. S.; Iyer, M. R.; Hester, S. K., II. *Org. Lett.* **2006**, *8*, 3113−3116.

[2] (a) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257−3260. (b) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935−9942.

[3] Kong, Y.-C.; Cheng, K.-F.; Cambie, R. C.; Waterman, P. G. *J. Chem. Soc., Chem. Commun.* **1885**, 47−48.

[4] Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809−8816.

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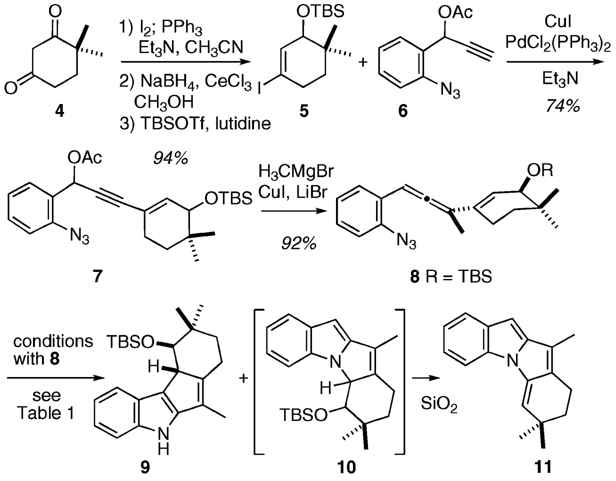
The initial foray into allenyl azide photochemistry did not provide promising results, Scheme 1, entry b. A nearly equal mixture of the C−C- and C−N-bonded products resulted from irradiation of the unadorned cyclohexenyl substrate **1** in CH_3CN (Rayonet photochemical reactor, 0.005 M, N_2 purge) for 2 h. Although photochemistry offered no advantage over thermolysis for this substrate, these results did demonstrate, for the first time, that the allenyl azide cyclization cascade could be triggered at lower temperatures through simple irradiation.

Extension of this photochemistry to the more highly functionalized substrate **8** led to surprising and irreproducible results: **9**/**11** regioisomer ratios from 1:1 to 6:1, depending upon batch (Scheme 2). This variability was traced to the presence of contaminants that survived chromatographic purification of the starting allene, which was formed in the presence of a large excess of cuprate reagent. Photochemical trials in the presence of $MgBr_2$, LiBr, and various copper salts, alone and in combination, eventually led to the observation that irradiation of **8** in the presence of stoichiometric (and greater) quantities of CuI reproducibly furnished tetracyclic product that was strongly biased toward the C−C-bonded regioisomer **9**, Table 1, entries c−f.

Scheme 2. Synthesis and Cyclization of Allenyl Azide Substrate **8**



This tetracyclic material was formed as a single stereoisomer whose relative stereochemistry was first suggested by analysis of ^1H coupling constants and later verified by single-crystal X-ray analysis[5] (see Supporting Information). The ether **10** did not survive SiO_2 chromatography, and only the dehydration product **11** could be recovered. The isolated yields of **9** and **11** did not always reflect the crude **9**/**10** ratios, as variable losses upon chromatography occurred, and so both sets of values are reported.

Is it the photochemistry or is it the copper? To probe this question, thermolysis of **8** in the presence of CuI was examined (Table 1, entries g−i). Indeed, the inclusion of CuI in the thermal process had the same favorable effect as in the photochemical series, but higher concentrations of substrate were necessary to achieve satisfactory results.

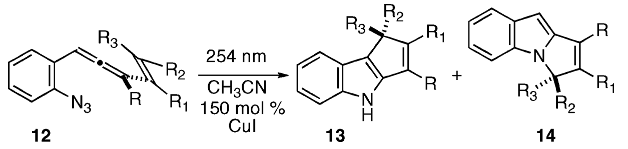
Table 1. Optimization of the Formation of C−C-Bonded Tetracycle **9** from Allenyl Azide **8**

entry	conditions^{a}	**9/10** ratio^{b}	**9** (%)^{c}	**11** (%)^{c}
a	110 °C	1:1.6	30	50
b	254 nm	1:1	33	34
c	254 nm, 50% CuI	4:1	51	16
d	254 nm, 80% CuI	6:1	62	10
e	254 nm, 120% CuI	9:1	61	6
f	**254 nm, 150% CuI**	**10:1**	**62**	**8**
g	110 °C, 150% CuI	1:1.6	31	44
h	110 °C, 150% CuI, 35 mM	3.5:1	48	18
i	110 °C, 150% CuI, 51 mM	5:1	52	13

^{a} CH_3CN solvent, 5 mM in **8** unless otherwise noted, quartz vessel for the irradiations; mol % CuI indicated. The temperature of the photochemical reaction solution was 30−35 °C. ^{b} From integration of diagnostic signals in the ^1H NMR spectrum of the crude reaction mixture. ^{c} Chromatographically pure material.

A survey of various allenyl azide substrates revealed that, with one exception, the high selectivity for C−C bond formation observed with **8** carries over to a range of substituent patterns, Table 2 and Schemes 2 and 3. The syntheses of the allenyl azide substrates examined in this study either were described earlier[1] or followed chemistry similar to that developed for **8** (see Supporting Information for experimental details). That the allylic oxygen function of **8** did not play a role in enhancing the regioselectivity of bond formation is implied by the cyclization results of the simple cyclohexenyl substrate **1** (Table 2, entry a; compare to Scheme 1), a species that proceeded to product with similar yield and indistinguishable regioselectivity as the allylic ether

Table 2. Copper-Mediated Photochemical Cyclization of Representitive Allenyl Azides



entry	R	R_1	R_2	R_3	**13/14** ratio^{a}	**13** (%)^{b}	**14** (%)^{b}
a	CH_3	$-(CH_2)_4-$		H	>10:1^{c}	54	
b	CH_3	Ph	H	H	>10:1^{c}	67	
c	CH_2OTBS	H	H	H	10:1	55	3
d^{d}	Ph	CH_3	H	H	> 10:1^{c}	69	
e	CH_3	Ph	Ph	Ph	2.2:1	53	26

^{a} From integration of diagnostic signals in the ^1H NMR spectrum of the crude reaction mixture. ^{b} Chromatographically pure material. ^{c} Estimated from ^1H NMR detection limits. ^{d} Irradiated at 300 nm.

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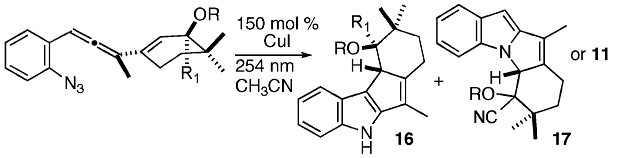
(5) Cambridge Crystallographic Data Centre deposition numbers: **9**, 650218; **14e**, 649706; **16b**, 652945; **22**, 651276. The data can be obtained free from the Cambridge Cyrstallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Copper Iodide-Mediated Photochemical Cyclization of Some Oxygenated Cyclohexenyl Allenyl Azides



15a R = TIPS R$_1$ = H	*69%*	**16a** R = TIPS R$_1$ = H	13:1 (14:1)[a]	**11**
15b R = TBS R$_1$ = CN	*69%*	**16b** R = TBS R$_1$ = CN	9:1 (10:1)[a]	**17**

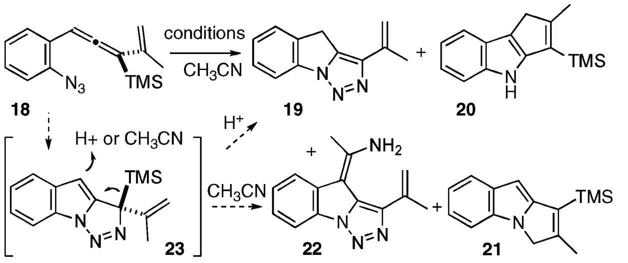
[a] Ratio of isolated, chromatographically pure material (^{1}H NMR ratio from the crude reaction mixture.

index case. Substrates **12b**, **12c**, and **12d** (Table 2, entries b−d) demonstrate that the cyclohexene ring plays no decisive role in the enhanced selectivity, as these simple alkene substrates also provide almost exclusively the C−C-bonded product **13**. Furthermore, entry c demonstrates that a functionalized variant of the allene substituent, R = CH$_2$OTBS (Table 2, entry c), is tolerated and furnishes only the C−C bonded product in measurable amounts. The last entry of Table 2 provides the first example of this cyclization cascade that fashions a C−C bond to a quarternary carbon. The structural assignment of **14e** derives from a single-crystal X-ray analysis[5] (see Supporting Information). This latter case is distinctive for two reasons: (1) There appears to be significant erosion in the regioselectivity for C−C bond formation even under the copper-mediated conditions (compare **12e** with *hν*/no copper, 1.9:1 **13e**/**14e**). (2) Substrate **12e** did not engage in undesired electrocyclizations of the allenyl-vinyl-(*Z*)-phenyl assembly, despite some indirect precedent for this type of process.[6] In contrast, substrates bearing a methyl group in the (*Z*)-alkenyl position did not survive long enough to test in the allenyl azide cyclization cascade, as they appeared to rearrange through [1,5] H-shifts.[7]

Two further examples of cyclohexenol-derived allenyl azide substrates were examined, Scheme 3. TIPS ether **15a** was designed to test the relationship between steric bulk at the allylic ether position and selectivity. The formation of a mixture of the C−C-bonded product **16a** and the elimination product **11** in a ratio even more favorable than the OTBS case **8** suggests that the regioselectivy may be susceptible to fine-tuning by peripheral steric influences. The stereochemistry of **16a** was assigned by comparison of its ^{1}H NMR spectral data to those of **9**, whose structural assignment was secured by X-ray analysis. The silylated cyanohydrin substrate **15b** delivered the expected C−C-bonded product **16b** as the strongly favored isomer as expected, but in this instance, elimination of OTBS from the C−N-bonded isomer **17** was not observed. Tetracycles **16b** and **17** were isolated as single stereoisomers; the relative stereochemistry of **16b** was ascertained by single-crystal X-ray analysis (see Supporting Information),[5] whereas the relative stereochemistry of **17** remains unassigned.

The silylated allene substrate **18** provides some insight into the possible role that copper plays in steering the product regiochemistry strongly toward the C−C-bonded product **20** (Scheme 4). Upon thermolysis with or without copper, **18** provides only a trace of **20** and none of the C−N-bonded regioisomer **21**. Rather, the aromatic triazole **19** predominates along with lesser amounts of the unexpected formal acetonitrile adduct **22** (structure by single-crystal X-ray analysis;[5] see Supporting Information). Apparently, the very nucleophilic allylic silane moiety of **23** is readily trapped by either adventitious protons (to form **19**) or, quite remarkably, by acetonitrile to provide **22**.[8] Upon irradiation without copper, all products observed can be rationalized by citing reaction through the expected [3 + 2] cycloaddition intermediate **23**, although the lower temperature of the photochemical reaction may suffice to minimize allylsilane reactivity. On the other hand, reaction of **18** under the copper-mediated photochemical conditions leads to a different result; formation of the C−C-bonded indole **20** as the major product accompanied by only traces of the triazole. The triazole in this instance may be formed by competitive non-copper-mediated chemistry, but the formation of **20** upon copper intercession clearly requires consideration of an alternative reaction course compared to the non-copper case.

Scheme 4. Silylated Allenyl Azide Substrate **18** Highlights the Distinct Consequences of Copper Mediation



	19	20	21	22
110 °C	*53%*	---	---	*23%*
110 °C/150 mol % CuI	*40%*	*3%*	---	*6%*
254 nm	*6%*	*28%*	*35%*	---
254 nm/150 mol % CuI	*8%*	*48%*	---	---

The role that copper might play in this complex transformation is illustrated with substrate **1** (Scheme 5). The key point of departure as a result of copper mediation may be the formation of the copper-bound indolidenes **25a**/**26a**. These species might originate through standard dipolar cycloaddition/N$_2$ extrusion to form **25**/**26**, followed by capture of the reactive indolidenes by ligated copper, or they might owe their genesis to an entirely different mechanistic course featuring a copper nitrene **28**[9] and a formal copper-

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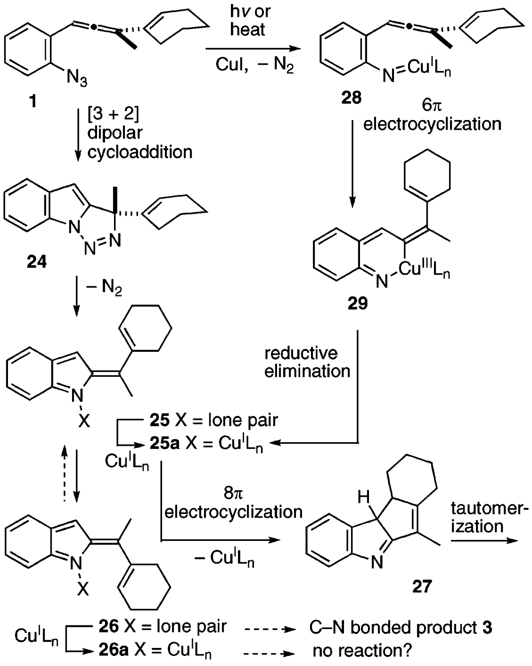
Scheme 5. Mechanistic Analysis of the Copper-Mediated Photochemical Cyclization of Allenyl Azides



(III) intermediate **29**.[10] The experimental results do not allow differentiation between these two pathways in the photochemical series, but the predominant formation of **19**/**22** from **18** under thermolysis/CuI is only consistent with operation of the former process.

Density functional theory calculations on a model system support this view (HCN instead of CH_3CN as a copper ligand, vinyl and proton as allene terminal substituents; see Supporting Information for calculational details and further discussion). In the absence of copper, prior calculations indicated that the indolidene pair **25**/**26** does not equilibrate faster than each electrocyclizes to product (**2** from **25** and **3** from **26**), and so the **2**/**3** product mixture reflects the relatively unbiased partitioning of **24** into **25** and **26**.[11] However, with copper present, calculations suggest that these energetics are perturbed. The activation energy for the conversion of the Cu−N-bound intermediate **26a** into **3**·CuL_n (not shown) is elevated substantially compared to the copper-free case (27 vs 18 kcal/mol, respectively), whereas the barrier for the **25a** → **27** cyclization is essentially insensitive to the presence of copper (ca. 15 kcal/mol). Furthermore, the calculated barrier to **25a**/**26a** equilibration (24 kcal/mol) is now lower than this **26a** cyclization value (27 kcal/mol). Thus, the notable advance of these studies, that photochemistry in the presence of CuI leads to high levels of selectivity for the C−C bond cyclopentannelated indole product, can be attributed to formation of a readily equilibrating pair of indolidene isomers **25a**/**26a** from which the *E* isomer **25a** proceeds to product much faster than the *Z* isomer **26a**.

In summary, the inclusion of CuI in the photochemical decomposition of 2-allenylphenyl azides diverts the complex cascade sequence down a mechanistic pathway that appears to be distinct from that of the non-copper-mediated process. High levels of regiochemical control for the C−C-bonded indole product can be achieved, possibly signifying the intermediacy of a copper nitrene species. Whereas the mechanistic intricacies still remain to be unraveled, the significant improvement in reaction regiochemistry may render this transformation useful in the synthesis of C(2)−C(3) cyclopentannelated indole natural products.

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Supporting Information Available: Full experimental details and spectroscopic data for **5**−**9**, **11**, **12d,e**, **13d,e**, **14e**, **15a,b**, **16a,b**, and **17**−**22**; X-ray crystallographic data and thermal ellipsoid polts for **9**, **14e**, **16b**, and **22**; computational details and energy level diagrams for Scheme 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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