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Dispersion-Controlled Regioselective Acid-Catalyzed Intramolecular Hydroindolation of *cis*-Methindolylstyrenes To Access Tetrahydrobenzo[*cd*]indoles

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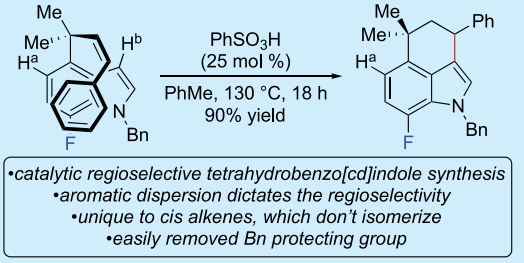
Supporting Information

ABSTRACT: Readily prepared *cis*-β-(α′,α′-dimethyl)-4′-methindolylstyrenes undergo acid-catalyzed intramolecular hydroindolation to afford tetrahydrobenzo[*cd*]indoles. Our experimental and computational investigations suggest that dispersive interactions between the indole and styrene preorganize substrates such that 6-membered ring formation is preferred, apparently via concerted protonation and C−C bond formation. When dispersion is attenuated (by a substituent or heteroatom), regioselectivity erodes and competing oligomerization predominates for *cis* substrates. Similarly, all *trans*-configured substrates that we evaluated failed to cyclize efficiently.



Substrate conformational biasing arising from steric constraints, such as those imposed by geminal dialkyl groups (i.e., the Thorpe−Ingold effect),[1] are often used to circumvent energetic barriers to bond formation in order to prepare new and useful molecules. We recently developed an intramolecular acid-catalyzed hydroarylation of β-(α′,α′-dialkyl)benzylstyrenes (**A**, Scheme 1A), showing that a *gem*-dialkyl group can be used to synthesize indanes efficiently (**B**).[2,3] We became interested in applying this design concept to more complex and medicinally relevant substrates, namely 4-bromoindole-derived β-(α′,α′-dimethyl)-4′-methindolylstyrenes like **C** (Scheme 1B), which are rapidly prepared by sequential enolate cross-coupling, Wittig, and benzyl protection reactions.[4] Cyclization could occur at either C3 to afford tetrahydrobenzo[*cd*]indole **D** or at C5 to afford tetrahydrocyclopenta[*e*]indole **E**. Herein, we report that a variety of 3-aryl-5,5-dimethyl-1,3,4,5-tetrahydrobenzo[*cd*]-indoles (**D**) are efficiently prepared in good yield by treating the *cis*-configured isomer of **C** with Brønsted acid catalysts (Scheme 1B, top pathway). In contrast, *trans*-configured substrates predominantly oligomerize (Scheme 1B, bottom pathway). Our experimental and computational data suggest that angle compression can induce a ground-state stabilization of *cis*-substrates through dispersive interactions, presumably between arene π systems,[5] enabling a concerted protonation and electrophilic attack to afford **G**, which rearomatizes to **H** (Scheme 1C).[6] A concerted mechanism avoids generating a long-lived carbocation intermediate that would be more likely to participate in competing intermolecular decomposition pathways, which may explain the disparate cyclizing ability of *trans*-configured starting materials and nondispersible *cis*-configured substrates (see below).

Products like **H** contain quaternary geminal dimethyl and diarylmethine motifs, which are well-represented in natural products and medicines,[7] and contain the 5,5-dimethyl-1,3,4,5-tetrahydrobenzo[*cd*]indole framework (in blue) common to the important ambiguine and hapalindole natural product families and closely related to lysergic acid.[8] Despite significant synthetic attention devoted to 5,5-dimethyl-1,3,4,5-tetrahydrobenzo[*cd*]indoles, a general method for their synthesis has not been reported. Target-oriented cyclization strategies have included stoichiometric Lewis acid mediated alkene hydroindolations using 7-methoxy-substituted 3-alkenylindoles[9] or additions to carbonyls[10] and intramolecular Heck reactions of 4-bromoindoles.[11]

Our optimization revealed that *cis*-configured indole analogues could be cyclized with good regioselectivity (85:15) favoring tetrahydrobenzo[*cd*]indole by using arene-containing Brønsted acid catalysts in non-Lewis basic polarizable aprotic solvents.[4] Good yield was obtained after heating for 24 h at 130 °C in the presence of 25 mol % of anhydrous benzenesulfonic acid in toluene. Under the optimized conditions, our evaluation of different N protecting groups revealed their influence on the yield and regioselectivity of the reaction (Table 1). The best result was obtained using *cis*-configured benzyl-protected substrate **1a**, which afforded 73% isolated yield of major product **2a** on 0.2 mmol scale (entry 1)

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Scheme 1. Geminal Dimethyl-Enabled Catalytic Intramolecular Alkene Hydroarylation Reactions

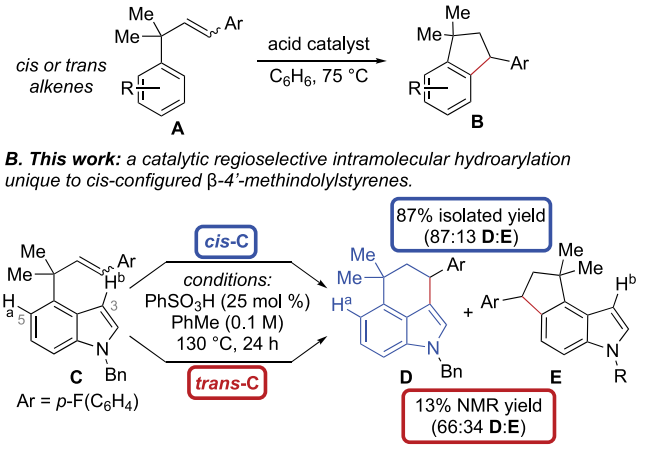
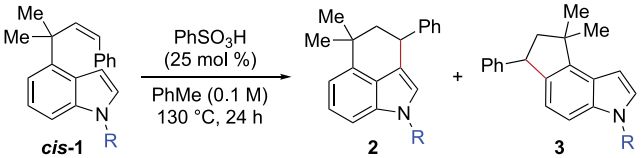


Table 1. Evaluation of Indole N-Protecting Groups*



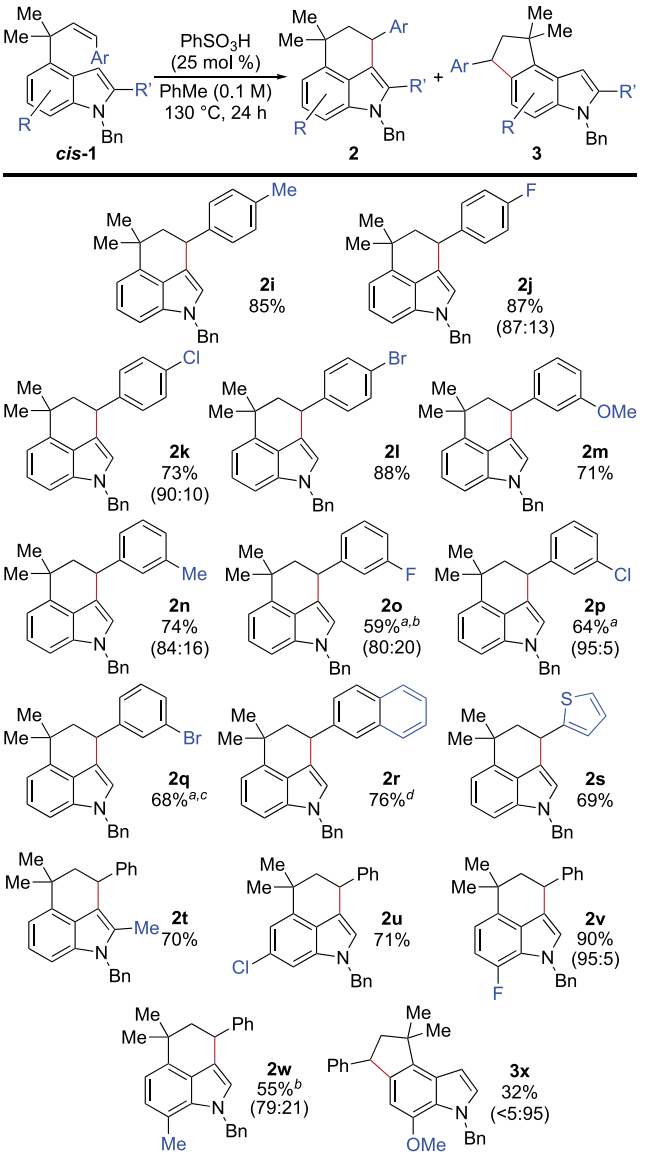
entry	substrate ID	R	conv. (%)	isolated yield (%) of **2**	rr (**2**:**3**)[a]
1	**1a**	Bn	100	73	85:15
2[b]	**1a**	Bn	100	69	85:15
3	**1b**	$C_2H_4SO_2Ph$	100	57	80:20
4	**1c**	Me	100	68	83:17
5	**1d**	Et	100	72	83:17
6[c]	**1e**	*i*-Pr	100	75	83:17
7	**1f**	Ts	100	72[d]	60:40
8	**1g**	Ac	<5	<5	n.d.
9[e]	**1h**	H	100	<5	n.d.

*Reactions were conducted on a 0.2 mmol scale in a closed vial unless otherwise noted. [a]Regioisomeric ratio determined by ^{1}H NMR analysis of the crude reaction. [b]Reaction was conducted on a 1.0 mmol scale. [c]Structure of **2e** confirmed by X-ray crystallography. [d]Combined yield of inseparable regioisomers. [e]Structure of **1h** confirmed by X-ray crystallography.

and a similar yield at 1.0 mmol scale (entry 2). The benzyl group in **2a** is readily deprotected in 91% yield.[12] Another readily deprotected indole, *N*-ethylsulfonyl analogue **1b**, afforded **2b** in slightly reduced yield and selectivity (entry 3).[13] Yields and regioselectivities for *N*-alkylindolyl substrates were similar to those of **1a** and include methyl (**1c**) ethyl (**1d**) and isopropyl (**1e**) groups (entries 4–6). When an electron-withdrawing tosyl protecting group was used, selectivity diminished (**1f**, entry 7). Acetyl protection prevented substrate conversion (entry 8). Lastly, free N–H indole **1h** simply decomposed (entry 9).

We next evaluated the influence of functional groups on the cyclization of *N*-benzylindolyl substrates (Scheme 2). Owing

Scheme 2. Scope of the Cyclization*



*Reactions employed pure *cis*-alkenyl starting materials unless otherwise noted and were conducted on a 0.2 mmol scale in a closed vial. The substrates were fully consumed in all cases. Unless otherwise noted, yields refer to the isolated indicated major product, and regioselectivities (**2**/**3**, indicated in parentheses) were determined by ^{1}H NMR analysis of the crude reaction. [a]80 mol % of $PhSO_3H$ was used. [b]Yield refers to an inseparable mixture of **2** and **3**. [c]Starting material was a 65:35 mixture of *cis* and *trans* isomers. [d]Starting material was a 78:22 mixture of *cis* and *trans* isomers.

to the generally good regioselectivity of the reaction (ranging from 80:20 to >95:5), we were typically able to obtain the fused tricyclic isomer in good or excellent yield. *Para*-substituents on the styrene moiety, including Me, F, Cl, and Br (**1i–l**), afforded fused tricycles in high yield, as did electron-donating groups positioned *meta*, like methoxy (**1m**) and methyl (**1n**). In contrast, stoichiometric amounts of

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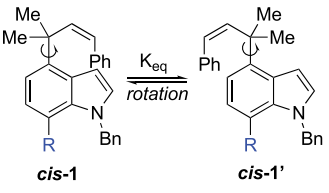
Table 2. Calculated Enthalpies of Substrate Rotamers[a]



substrate	R	ΔΔH (kcal/mol)	K_{eq} (130 °C)
1v	F	6.66	2.5×10^{-4}
1a	H	5.36	1.2×10^{-3}
1w	Me	4.95	2.1×10^{-3}
1x	OMe	3.54	1.4×10^{-2}

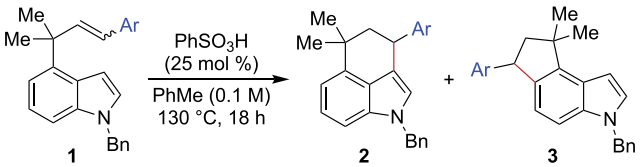
[a]Gas-phase calculations of $\Delta\Delta H$ using B3PW91/6-311G(d) with the GD3 empirical dispersion correction.

benzenesulfonic acid are required to obtain acceptable yields when halogens are positioned *meta* to the alkene (**1o–q**); *m*-bromo substrate **1q** cyclized in 68% yield from an inseparable 65:35 mixture of *cis* and *trans* isomers. Beyond substituted benzenes, we found that 2-naphthyl analogue **1r** gave 76% yield of **2r** from a 78:22 mixture of *cis* and *trans* starting stereoisomers, respectively. In our final variation of the alkene aromatic substituent, a 2-thiophene analogue also afforded the fused tricycle **2s** in good yield. Shifting our focus to functional group tolerance on the indole ring, a 2-methyl substituent was well-tolerated, as were 6-chloro and 7-fluoro variants (**2t–v**, respectively). The latter afforded the best yield and regioselectivity that we observed in this study. Surprisingly, adding electron-donating substituents to the 7 position impacted the regioselectivity significantly, with 7-methyl substrate **1w** affording a 55% yield of an inseparable regioisomeric mixture of **2w** and **3w**. Even more surprisingly, formation of the 6-membered ring was completely prohibited by the presence of a 7-methoxy substituent—only **3x** was isolated.

The disparate regioselectivity outcomes for substrates **1v–x** imply a high degree of dependence on the electronic nature of the indole ring. We hypothesized that this could be due to the Thorpe–Ingold effect inducing overlap between the indole and styrene, which would necessarily deconjugate the styrenyl alkene. As an indirect measure of the distortion of the C=C bond, we computed the relative gas phase enthalpies ($\Delta\Delta H$) of the two rotamers (*cis*-**1** and *cis*-**1′**) of 7-substituted indole substrates that would lead to the respective products **2** or **3** using B3PW91/6-311G(d) with the GD3 empirical dispersion correction (Table 2).[14] (Note: the computed rotamer enthalpies do not differ significantly without GD3 correction.[4]) Fluorinated rotamer *cis*-**1v** is 6.66 kcal/mol more stable than rotamer *cis*-**1v′** (incidentally corresponding to an equilibrium constant favoring *cis*-**1v** by a factor of over 4000 at 130 °C). As R becomes more electron rich, dispersion is attenuated ($\Delta\Delta H$ diminishes). Greater dispersion appears to facilitate alkene protonation, hypothetically by attenuating the alkene's conjugation to the phenyl ring.

In contrast to *cis* alkenes (odd-numbered entries, Table 3), *trans* alkenes (even-numbered entries) afford uniformly low yields and reduced regioselectivities, presumably due to the absence of dispersion (see the Supporting Information for *trans* enthalpies). Further, while nonindolic *cis*-*β*-benzylstyrene *cis*-**A** isomerizes to *trans*-**A** in just 1 h at 80 °C (Scheme 3A), indole analogue ***cis*-1c** is unreactive after 24 h (Scheme 3B).

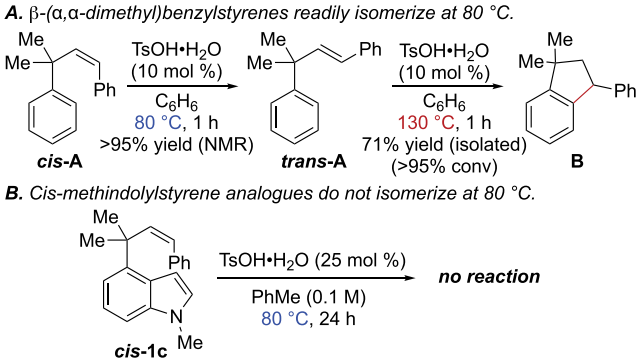
Table 3. Influence of *cis*- and *trans*-Alkene Configuration on the Cyclization of Methindolylstyrenes*



entry	substrate ID	Ar	NMR yield (%, **2**+**3**)[a]	rr (**2**:**3**)[a]
1	***cis*-1j**	*p*-F(C_6H_4)	99	87:13
2	***trans*-1j**		13	66:34
3	***cis*-1k**	*p*-Cl(C_6H_4)	81	90:10
4	***trans*-1k**		32	60:40
5	***cis*-1n**	*m*-Me(C_6H_4)	88	84:16
6	***trans*-1n**		37	65:35
7[b]	***cis*-1p**	*m*-Cl(C_6H_4)	69	95:5
8[b]	***trans*-1p**		10	n.d.

*Reactions were conducted on a 0.2 mmol scale in a closed vial and substrates were consumed in full in all cases. The major decomposition pathway for *trans* substrates is oligomerization. [a]Yield and regioselectivity were determined by ^{1}H NMR analysis of the crude reaction mixture. [b]80 mol % of catalyst was used.

Scheme 3. Disparate Behavior of *cis*-*β*-Benzylstyrene and *cis*-*β*-4′-Methindolylstyrene



Combined with our DFT data, these configurational reactivity differences suggest that dispersion-induced deconjugated alkenes undergo concerted hydroindolation, since *cis* alkenes resist isomerization to *trans* alkenes despite the cation-promoting conditions. Incidentally, *trans*-**A** cleanly cyclizes to indane **B** by increasing the reaction temperature to 130 °C (Scheme 3A), perhaps due to sufficiently fast five-membered ring formation.

We also found that benzothiophene analogue *cis*-**4** cyclizes with regioselectivity similar to indoles under identical conditions, albeit a bit more sluggishly. In contrast, *trans*-**4** cyclized with slightly improved yield and regioselectivity compared to *trans* indoles (eq 1). In contrast, we did not observe formation of the corresponding fused tricycle when using benzofuran analogues (eq 2). Rather, *cis*-**7** isomerized to *trans*-**7** at just 80 °C, with some formation of regioisomer **8** observed. This disparate behavior compared to indoles and benzothiophenes is likely due to a combination of diminished nucleophilicity at C3 and diminished dispersion (our DFT calculations show $\Delta\Delta H$ = 3.16 kcal/mol for the two *cis* rotamers of **7**).[4]

In conclusion, we have developed a catalytic intramolecular alkene hydroindolation to construct medicinally significant

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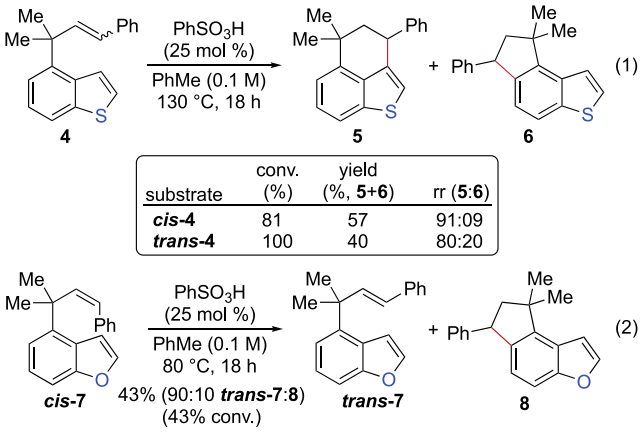

tetrahydrobenzo[*cd*]indoles from *cis*-methindolylstyrenes bearing a benzylic *gem*-dimethyl group, putatively via a concerted protonation and C−C bond formation. Empirical trends (substrate isomerizability, regioselectivity outcomes, electronic sensitivity, and temperature profile) and calculated ground-state enthalpies suggest that the regioselectivity is dependent on dispersive interactions between the styrene and indole, which are forced into proximity by the *gem* dimethyl.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00043.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 1884246−1884247 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

A prior version of this work was previously published on ChemRxiv.[15]

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■ REFERENCES

(1) For a recent review, see: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

(2) Cai, X.; Keshavarz, A.; Omaque, J. D.; Stokes, B. J. *Org. Lett.* **2017**, *19*, 2626.

(3) For recent alkene hydroarylations, see: (a) Minami, Y.; Noguchi, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2017**, *139*, 14013. (b) Niharika, P.; Satyanarayana, G. *Eur. J. Org. Chem.* **2018**, *2018*, 971. For relevant reviews, see: (c) Rueping, M.; Nachtsheim, B. J.; Beilstein. *Beilstein J. Org. Chem.* **2010**, *6*, 6. (d) Naredla, R. R.; Klumpp, D. A. *Chem. Rev.* **2013**, *113*, 6905. For recent electrophilic carbocyclization methods, see: (e) Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8851. (f) Li, A.; DeSchepper, D. J.; Klumpp, D. A. *Tetrahedron Lett.* **2009**, *50*, 1924.

(4) See the Supporting Information for details.

(5) For reviews on the role of dispersive aromatic interactions in organic reactions, see: (a) Maji, R.; Wheeler, S. E. In *Aromatic Interactions: Frontiers in Knowledge and Application*; The Royal Society of Chemistry, 2017; pp 18−38. (b) Wagner, J. P.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 12274. (c) Wheeler, S. E.; Bloom, J. W. G. *J. Phys. Chem. A* **2014**, *118*, 6133. (d) Wheeler, S. E. *Acc. Chem. Res.* **2013**, *46*, 1029. For new methods leveraging dispersive intramolecular aromatic interactions, see: (e) Mishra, S.; Liu, J.; Aponick, A. *J. Am. Chem. Soc.* **2017**, *139*, 3352.

(6) For examples of concerted cationic alkene functionalization reactions, see: (a) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, *134*, 11992. (b) Williams, A. *Concerted Organic and Bioorganic Mechanisms*; CRC Press: Boca Raton, 2000. (c) Haven, T.; Kubik, G.; Haubenreisser, S.; Niggemann, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4016. (d) Ghigo, G.; Maranzana, A.; Tonachini, G. *J. Org. Chem.* **2013**, *78*, 9041. (e) Vidhani, D. V.; Cran, J. W.; Krafft, M. E.; Alabugin, I. V. *Org. Biomol. Chem.* **2013**, *11*, 1624. (f) McCulley, C. H.; Geier, M. J.; Hudson, B. M.; Gagné, M. R.; Tantillo, D. J. *J. Am. Chem. Soc.* **2017**, *139*, 11158.

(7) For leading reports, see: (a) Lian, Y.; Burford, K.; Londregan, A. T. *Tetrahedron* **2015**, *71*, 9509. For a recent review, see: (b) Talele, T. T. *J. Med. Chem.* **2018**, *61*, 2166.

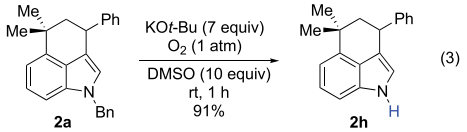
(8) Maimone, T. J.; Ishihara, Y.; Baran, P. S. *Tetrahedron* **2015**, *71*, 3652.

(9) Dethe, D. H.; Sau, S. K.; Mahapatra, S. *Org. Lett.* **2016**, *18*, 6392.

(10) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331.

(11) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.

(12) Benzyl deprotection was accomplished following the procedure developed by Deaton−Rewolinski and co-workers: Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett.* **2002**, *43*, 399.



(13) For the development of the *N*-ethylsulfonyl indole protecting group, see: Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J.; Muthusamy, S.; Swann, E. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 672.

(14) Frisch, M. J. et al. *Gaussian Development Version*, Revision I10; Gaussian, Inc.: Wallingford, CT, 2016. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Wang, Y.; Perdew, J. P. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1991**, *43*, 8911. (d) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104. (e) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.

(15) Cai, X.; Tohti, A.; Ramirez, C.; Harb, H.; Hratchian, H. P.; Stokes, B. J. *ChemRxiv* **2018**, DOI: 10.26434/chemrxiv.7397492.

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