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A Mechanistic Switch from Homoallylation to Cyclopropylcarbinylation of Aldehydes

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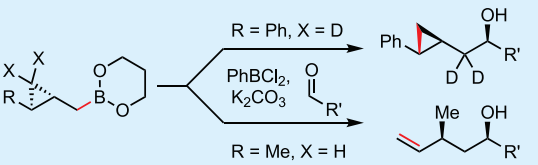
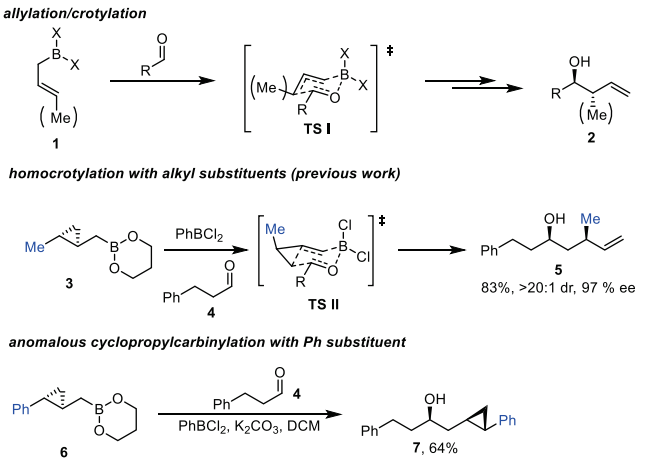
ABSTRACT: Cyclopropanated allylboration reagents participate in homoallylation reactions of aliphatic and aromatic aldehydes, generating allylic-substituted alkenes that are difficult to produce via other methods. In studying the effect of cyclopropane substituents, we discovered that an aryl substituent completely changes the outcome to cyclopropylcarbinylation, as if the cyclopropylcarbinyl fragment were transferred intact. However, density functional theory computation suggested a novel mechanism involving ring opening and reclosure, which is supported by experimental evidence.

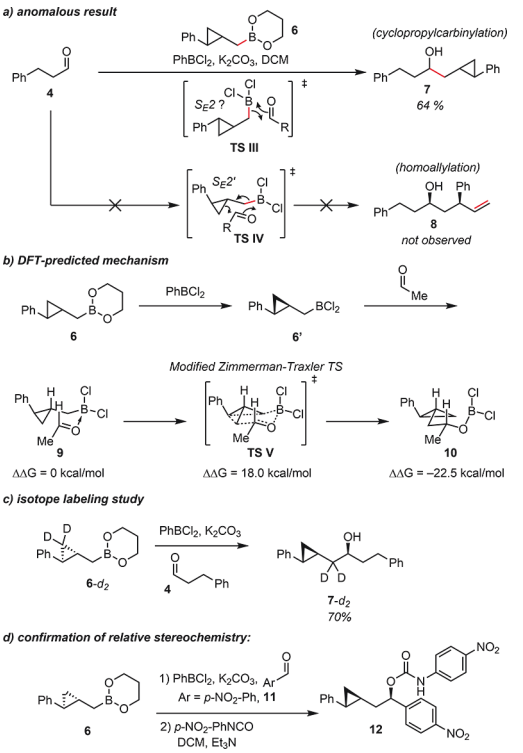


Allylboration and crotylboration of aldehydes are well-studied reactions, and a variety of asymmetric variants have been developed, taking advantage of well-organized closed transition states that result in predictable stereochemical outcomes (Scheme 1).[1] However, homoallylation and homocrotylation reactions are less developed.[2] Our group has prepared cyclopropanated allylboration reagents (cyclopropylcarbinylboronates), which homoallylate aldehydes through Zimmerman−Traxler transition states[3] that are apparently analogous to allylboronates (**TS-I**, **TS-II**).[4] During the course of a substituent scope investigation (see the preceding manuscript), we observed an anomalous result that has led us to a revised mechanistic hypothesis.[5] While substitution of an alkyl group at the γ-position of the boronate has led to alkyl-containing "homocrotylation" products with high stereospecificity (Scheme 1), we were surprised to

Scheme 1. Allylboration Versus Homoallylation with Cyclopropanated Allylboron Reagents



Scheme 2. Cyclopropylcarbinylation and Mechanistic Study



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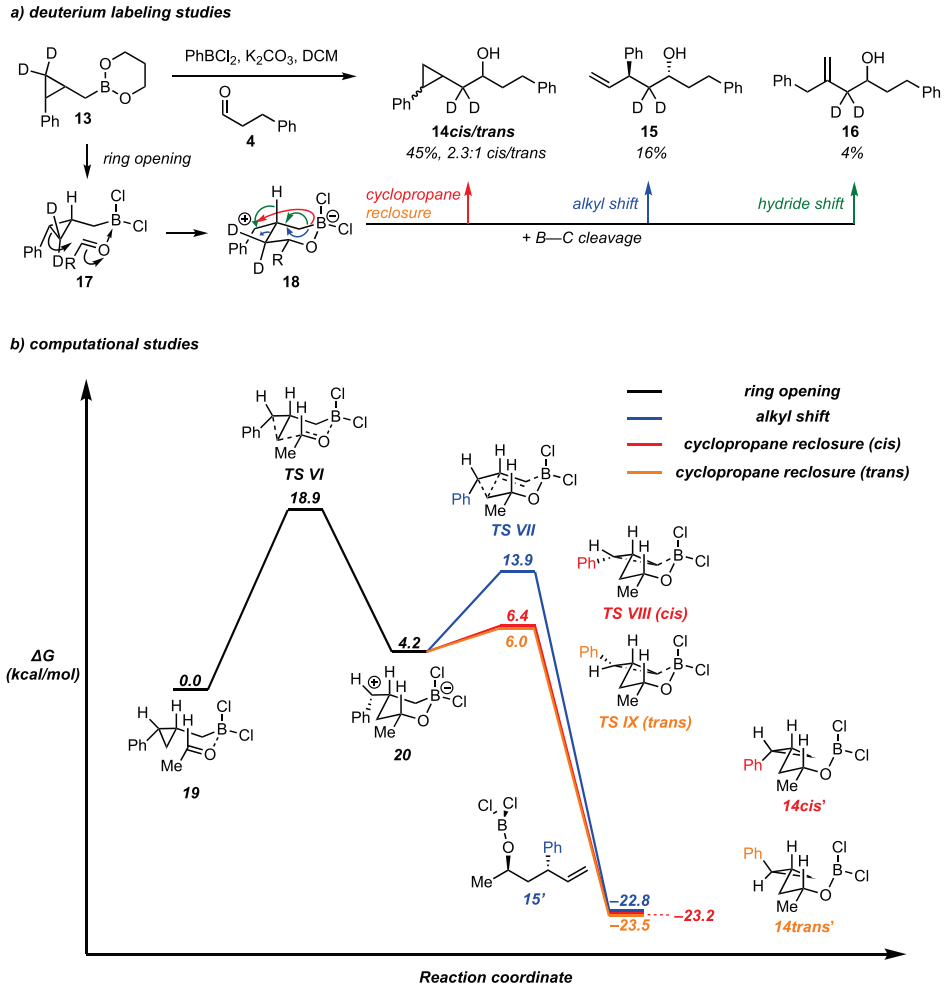
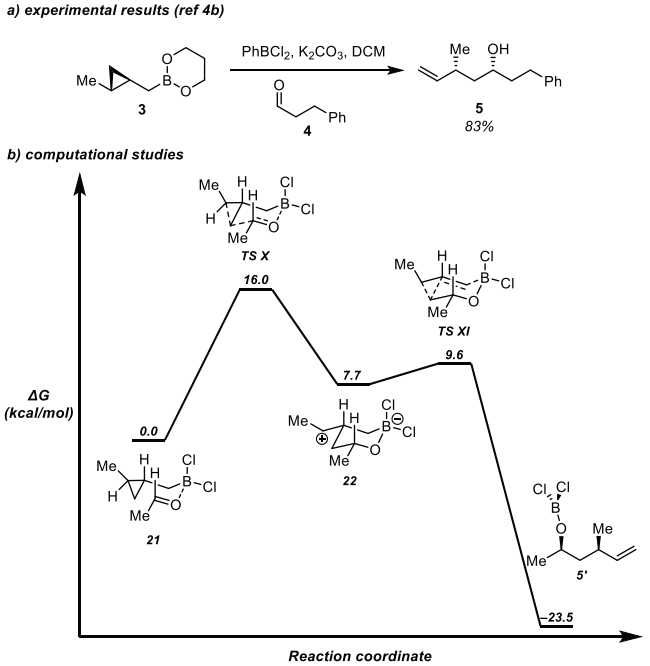
Scheme 3. Cyclopropylcarbinylation Versus Homoallylation with *cis*-Phenyl Reagent 13



Scheme 4. Homoallylation with *trans*-Methyl Reagent 3



observe that substitution of a phenyl group at this position led to cyclopropylcarbinylation (**6** → **7**). Herein, we present mechanistic evidence that this transformation occurs through cyclopropane ring opening and reclosure.

To explore potential mechanisms for this anomalous result, we undertook density functional theory (DFT) calculations (ωB97X-D/6-311++G(d,p)/SMD (CH_2Cl_2))[6] (see Scheme 2). Interestingly, the dichloroborane intermediate **6′** derived from $PhBCl_2$ activation of **6** was predicted to react through modified Zimmerman−Traxler transition state **TS-V**, in which the cyclopropane breaks and reforms in a concerted asynchronous fashion. To test this prediction experimentally, we prepared the deuterium-labeled reagent **6**-d_2. Consistent with the DFT-predicted mechanism, the deuterated methylene in the cyclopropane of boronate **6**-d_2 was replaced by a nondeuterated methylene in the cyclopropane of product **7**-d_2. To assign the relative stereochemistry of **7**, a crystalline analogue was prepared; *p*-nitrobenzaldehyde (**11**) reacted in good yield and was further derivatized as nitrophenylcarbamate **12**. The X-ray crystal structure of **12** (Figure S1 in the Supporting Information (SI)) showed that the relative stereochemistry of the cyclopropylcarbinylation product was consistent with the DFT-predicted mechanism, in which the aldehyde substituent is oriented equatorially in the chair transition state **TS-V**.

To further study the effect of the aromatic substituent, we prepared a *cis* analogue of **6**-d_2 (**13**, Scheme 3a). This reagent

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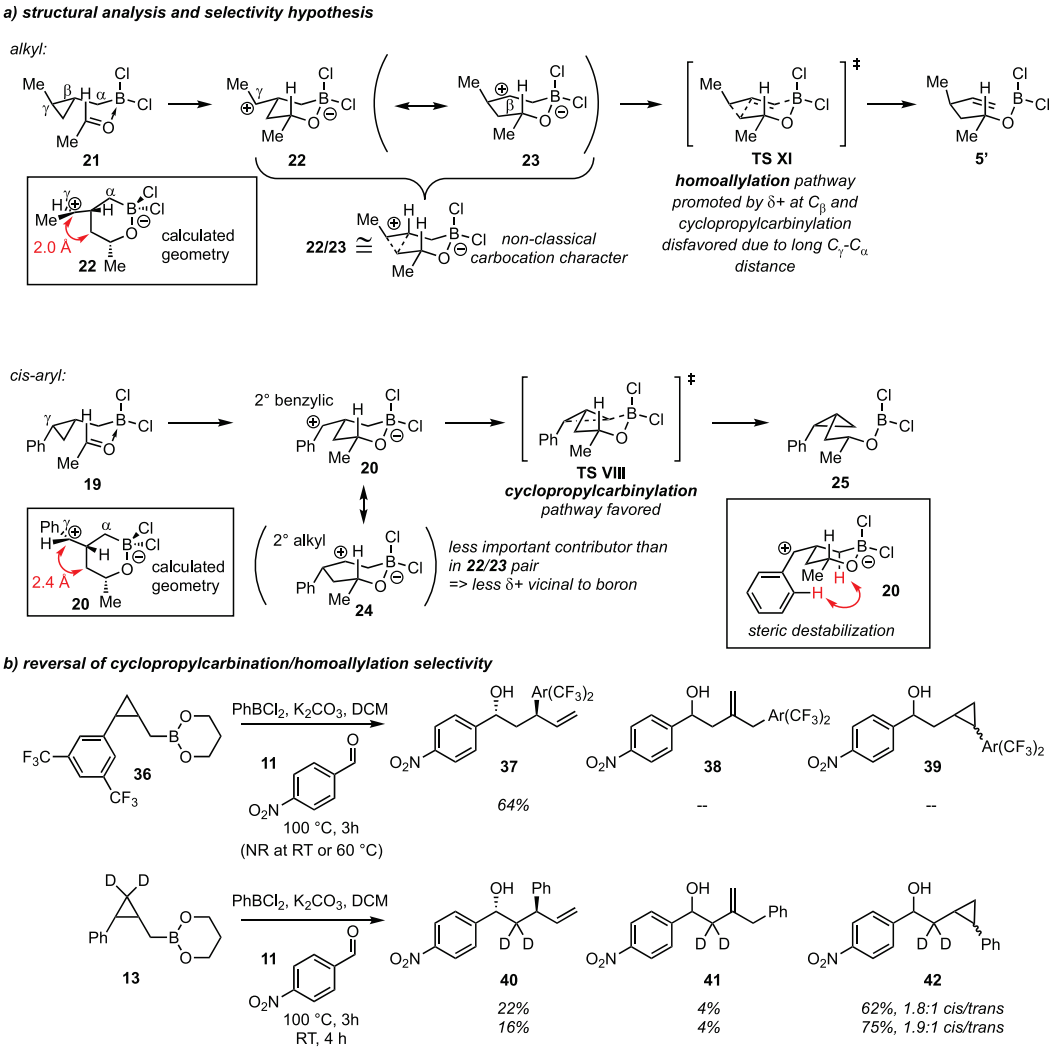
Scheme 5. Reversal of the Cyclopropylcarbinylation/Homoallylation Selectivity by Electronic Tuning



afforded the analogous cyclopropylcarbinylation product **14**, but, in this case, as a 2.3:1 *cis*/*trans* cyclopropane mixture. Interestingly, some homoallylation product **15** was also obtained, as well as a small amount of 1,1-disubstituted alkene **16**. The position of the deuterium labels was again consistent with a cyclopropane opening/closing mechanism, but, in this case, the presence of hydride shift product **16** and some *cis* → *trans* isomerization of the cyclopropane suggested a carbocationic intermediate. In fact, DFT calculations (ωB97X-D/6-311++G(d,p)/SMD (CH_2Cl_2)) (Scheme 3b) also predicted the cationic intermediate. According to the calculations, *cis* reagent **13** reacts through a slightly higher initial activation barrier than *trans* reagent **6** (ΔG = 18.9 kcal/mol, vs 18.0 kcal/mol); however, instead of a barrierless reclosure of the cyclopropane, the *cis* reagent recloses the ring through a second energy maximum **TS-VIII** (ΔG = 6.4 kcal/mol) to afford **14*cis***. The benzylic carbocation intermediate **20** (ΔG = 4.2 kcal/mol) between these two maxima can alternatively reclose cyclopropane with concomitant rotation of the phenyl ring (**TS-IX**, ΔG = 6.0 kcal/mol) to afford **14*trans***. To form the observed minor homoallylation product **15**, cation **20** is predicted to undergo a concerted carbon migration/B−C bond cleavage step (**TS-VII**, ΔG = 13.9 kcal/mol).

To probe the mechanistic factors that could favor homoallylation versus cyclopropylcarbinylation pathways, we used analogous DFT calculations (ωB97X-D/6-311++G(d,p)/SMD (CH_2Cl_2)) to evaluate the reaction pathway of known methyl-substituted reagent (**3**; see Scheme 4a). Although previous DFT calculations in the gas phase had suggested a concerted transition state (**TS II**, Scheme 1),[4b] the current computational method, including a solvation model, suggested a two-step pathway. After a ring opening transition state **TS X** (ΔG = 16.0 kcal/mol; see Scheme 4b) that is slightly lower in energy than **TS V**, a carbocation intermediate **22** is formed at 7.7 kcal/mol, but, in this case, the alkyl shift/B−C cleavage step (**TS-XI**) has a lower barrier than that in the *cis*-phenyl analogue ($\Delta\Delta G$ = 1.9 kcal/mol, versus 9.7 kcal/mol; see Schemes 3b and 4b). In **22**, the secondary carbocation center is only 2.0 Å from the methylene to which it was previously bonded (as opposed to 2.4 Å for benzylic carbocation **20**) and the adjacent methine carbon is distorted from a tetrahedral geometry. Together, these measurements suggest some nonclassical character in this carbocation; i.e., **22** leans toward an alkyl shift along the trajectory leading to the observed homoallylation product **5′** (Scheme 5a). Therefore, the homoallylation preference observed with alkyl-substituted reagents may reflect the tendency of the initially formed

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carbocation to undergo alkyl shift (2° → 2°), whereas benzylic cation **20** is more stable than secondary alkyl cation **24** and lacks this tendency, favoring attack by the B−C electron pair directly at the benzylic carbocation. Note that the DFT calculations overestimate the energy of a homoallylation pathway, compared with cyclopropylcarbinylation (Figures S2 and S3 in the SI) both for phenyl and methyl substituents; the observed homoallylation/cyclopropylcarbinylation ratios (1:2.8 for **15**/**14** and only homoallylation for **5**) are higher than those expected from the calculated energies. However, the calculations are qualitatively consistent with the observation that homoallylation is more favored with the alkyl substituent versus aryl.

Based on the calculated geometry for *cis*-phenyl-derived intermediate **20**, we noted that some destabilization may result from steric interactions between the phenyl ring and the methylene attached to boron (Scheme 5a, red hydrogens). We hypothesized that this destabilization may contribute to disfavoring cyclopropylcarbinylation with **13**, but not *trans* reagent **6**. To test whether further destabilization of the benzylic cation could shift the balance in favor of homoallylation, we prepared the boronate analogue **36** containing electron-poor arene (Scheme 5b). Although heating was required for any reaction to occur with nitrobenzaldehyde (**11**), homoallylation product **37** was isolated exclusively with 64% yield, with no cyclopropylcarbinylation product **39** or hydride-shift-derived **38**. By comparison, **13** afforded 62% cyclopropylcarbinylation product **42** with the same aldehyde. Control experiments with **13** showed that temperature was not responsible for the change in selectivity.

In summary, we have discovered and mechanistically characterized a selectivity switch that occurs in alkyl- versus aryl-substituted cyclopropylcarbinylboron reagents. Whereas alkyl substituents are compatible with homoallylation, aromatic substituents alter the course of the reaction, promoting cyclopropylcarbinylation through a ring-opening/ring-closing mechanism, and this effect can be reversed with electron-withdrawing arene substituents. Together with computational studies, these data suggest that the balance between these two pathways is dependent on the stabilization of cationic character on the cyclopropane carbon γ to boron.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01790.

Experimental procedures, computational data, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 2153772 contains 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.

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■ REFERENCES

(1) (a) Yamamoto, Y.; Asao, N. Selective reactions using allylic metals. *Chem. Rev.* **1993**, *93* (6), 2207−2293. (b) Denmark, S. E.; Fu, J. Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones. *Chem. Rev.* **2003**, *103* (8), 2763−2794. (c) Lachance, H.; Hall, D. G. Allylboration of Carbonyl Compounds. *Org. React.* **2009**, *73*, DOI: 10.1002/0471264180.or073.01.

(2) (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. Novel Stereoselective Cyclization via. pi.-Allylnickel Complex Generated from 1,3-Diene and Hydride Nickel Complex. *J. Am. Chem. Soc.* **1994**, *116* (21), 9771−9772. (b) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. Novel and Highly Regio- and Stereoselective Nickel-Catalyzed Homoallylation of Benzaldehyde with 1,3-Dienes. *J. Am. Chem. Soc.* **1998**, *120* (16), 4033−4034. (c) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. Nickel-Catalyzed Homoallylation of Aldehydes and Ketones with 1,3-Dienes and Complementary Promotion by Diethylzinc or Triethylborane. *Angew. Chem., Int. Ed.* **1999**, *38* (3), 397−400. (d) Sato, Y.; Takimoto, M.; Mori, M. Further Studies on Nickel-Promoted or -Catalyzed Cyclization of 1,3-Diene and a Tethered Carbonyl Group. *J. Am. Chem. Soc.* **2000**, *122* (8), 1624−1634. (e) Kimura, M.; Ezoe, A.; Tanaka, S.; Tamaru, Y. Nickel-Catalyzed Homoallylation of Aldehydes in the Presence of Water and Alcohols. *Angew. Chem., Int. Ed.* **2001**, *40* (19), 3600−3602. (f) Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. Nickel-Catalyzed Intermolecular Coupling of 1,3-Dienes and Aldehydes via Transmetalation of Nickelacycles with Diisobutylaluminum Acetylacetonate. *J. Org. Chem.* **2002**, *67* (3), 656−662. (g) Kimura, M.; Ezoe, A.; Mori, M.;

Iwata, K.; Tamaru, Y. Regio- and Stereoselective Nickel-Catalyzed Homoallylation of Aldehydes with 1,3-Dienes. *J. Am. Chem. Soc.* **2006**, *128* (26), 8559−8568. (h) Li, H.; Wu, J.; Luo, J.; Dai, W.-M. A Concise Total Synthesis of Amphidinolide T2. *Chem. - Eur. J.* **2010**, *16* (38), 11530−11534.

(3) Zimmerman, H. E.; Traxler, M. D. The Stereochemistry of the Ivanov and Reformatsky Reactions. I. *J. Am. Chem. Soc.* **1957**, *79* (8), 1920−1923.

(4) (a) Pei, W.; Krauss, I. J. Homoallylboration and Homocrotylboration of Aldehydes. *J. Am. Chem. Soc.* **2011**, *133* (46), 18514−18517. (b) Lin, H.; Pei, W.; Wang, H.; Houk, K. N.; Krauss, I. J. Enantioselective Homocrotylboration of Aliphatic Aldehydes. *J. Am. Chem. Soc.* **2013**, *135* (1), 82−85. (c) Dugas, G. J.; Lam, Y.-h.; Houk, K. N.; Krauss, I. J. Boron Carboxylate Catalysis of Homoallylboration. *J. Org. Chem.* **2014**, *79* (10), 4277−4284. (d) Lin, H.; Tian, L.; Krauss, I. J. Enantioselective syn and anti Homocrotylation of Aldehydes: Application to the Formal Synthesis of Spongidepsin. *J. Am. Chem. Soc.* **2015**, *137* (40), 13176−13182. (e) Tian, L.; Krauss, I. J. Stereoselective Homocrotylation of Aldehydes: Enantioselective Synthesis of Allylic-Substituted Z/E-Alkenes. *Org. Lett.* **2018**, *20* (21), 6730−6735.

(5) Polyak, D.; Xu, B.; Krauss, I. J. Homoallylboration of Aldehydes: Stereoselective Synthesis of Allylic-Substituted Alkenes and E-Alkenes. *Org. Lett.*, DOI: 10.1021/acs.orglett.2c01789.

(6) (a) Chai, J.-D.; Head-Gordon, M. Long-range corrected hybrid density functionals with damped atom−atom dispersion corrections. *Phys. Chem. Chem. Phys.* **2008**, *10* (44), 6615−6620. (b) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113* (18), 6378−6396.

https://doi.org/10.1021/acs.orglett.2c01790
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