JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Electric-Field-Assisted Anion–π Catalysis

Masaaki Akamatsu, Naomi Sakai, and Stefan Matile*

Department of Organic Chemistry, University of Geneva, 1211 Geneva, Switzerland

Supporting Information

ABSTRACT: This report focuses on the remote control of anion–π catalysis by electric fields. We have synthesized and immobilized anion–π catalysts to explore the addition reaction of malonic acid half thioesters to enolate acceptors on conductive indium tin oxide surfaces. Exposed to increasing electric fields, anion–π catalysts show an increase in activity and an inversion of selectivity. These changes originate from a more than 100-fold rate enhancement of the disfavored enolate addition reaction that coincides with an increase in selectivity of transition-state recognition by up to −14.8 kJ mol^{-1}. The addition of nitrate with strong π affinity nullified (IC_{50} = 2.2 mM) the responsiveness of anion–π catalysts to electric fields. These results support that the polarization of the π-acidic naphthalenediimide surface in anion–π catalysts with electric fields increases the recognition of anionic intermediates and transition states on this polarized π surface, that is, the existence and relevance of electric-field-assisted anion–π catalysis.

Conventional aromatic planes have an electron-rich π surface that attracts cations.[1] To bind anions rather than cations on π surfaces, an inversion of the quadrupole moment perpendicular to the aromatic planes, from Q_{zz} < 0 B to Q_{zz} > 0 B, is necessary (Figure 1).[2−4] This is possible with electron-withdrawing substituents, which in turn add in-plane multipoles that further support anion–π interactions (Figure 1a). The functional relevance of anion–π interactions has been indicated first in 2006 for anion transport.[5] Expanding the scope of anion–π stabilization from the ground state to the transition state, explicit anion–π catalysis was reported first for Kemp elimination reaction in 2013.[6] Since then, anion–π catalysis has been demonstrated in enolate, enamine, iminium, transamination and oxocarbenium chemistry, and the first anion–π enzyme has been created.[7,8]

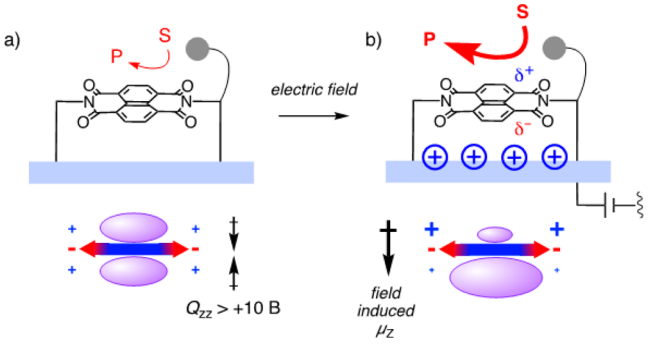

Figure 1. Concept of electric-field-assisted anion–π catalysis. (a) Bifunctional anion–π catalysts composed of, for example, a π-acidic NDI with Q_{zz} > +10 B and an amine base (gray circle) are immobilized on conducting surfaces (light blue). (b) Application of an electric field induces macrodipole μ_z, which in turn increases the stabilization of anionic intermediates and transition states between substrate S and product P on the polarized π surface of the catalyst.

The design of anion–π catalysts has so far focused on π acidity, i.e., the variation of Q_{zz} > 0 B. These studies have demonstrated the importance of a Q_{zz} > +10 B to achieve significant function.[9] However, computational studies have suggested early on that not only Q_{zz} but also the polarizability of the aromatic system contributes significantly to anion–π interactions.[3] Anion binding itself on the π surface produces a supportive induced dipole μ_z. Significantly increased anion–π interactions are also expected from polarization of the π-acidic surface by face-to-face π stacking with other aromatic systems.[3] Pioneering computational studies further suggested that polarization by electric fields will increase anion–π interactions.[4] Electric fields and potentials have been shown to accelerate reactions and activate conventional catalysts,[10] enzymes,[11] and catalytic pores[12] and to modulate the formation of dynamic covalent bonds,[13] DNA duplexes,[14] and ion pairs.[15] Here, we introduce electric-field-assisted anion–π catalysis.

To elaborate on remote control with electric fields, anion–π catalysts had to be immobilized on conducting surfaces. The application of an electric field was then expected to polarize the π-acidic aromatic system and convert the Q_{zz} > +10 B into an induced dipole μ_z (Figure 1). The tightened binding of anionic intermediates and transition states on this polarized π surface should then be reflected in increased catalytic activity. To elaborate on these expectations, we designed, synthesized and evaluated the heterogeneous anion–π catalyst **1** (Figure 2). The proposed bifunctional motif combines the privileged π-acidic surface offered by naphthalenediimides (NDIs, Q_{zz} ≈ +18 B)[5] with a tertiary amine. Interfacing with a conformationally constrained Leonard turn has been shown to be perfect to run reactions on aromatic surfaces.[8] For immobilization of this bifunctional catalyst on ITO surfaces, diphosphonate feet[16] were introduced via sulfide substituents in the NDI core. Details on the synthesis of precatalyst **2** can be found in the SI.[17]

Incubation of ITO electrodes with precatalyst **2** afforded the heterogeneous anion–π catalyst **1**. After 1 day of incubation, the oxidation of aqueous ferrocyanide was completely inhibited (Figure 2b). This suggested that the surface of the ITO

Received: March 10, 2017

DOI: 10.1021/jacs.7b02421
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

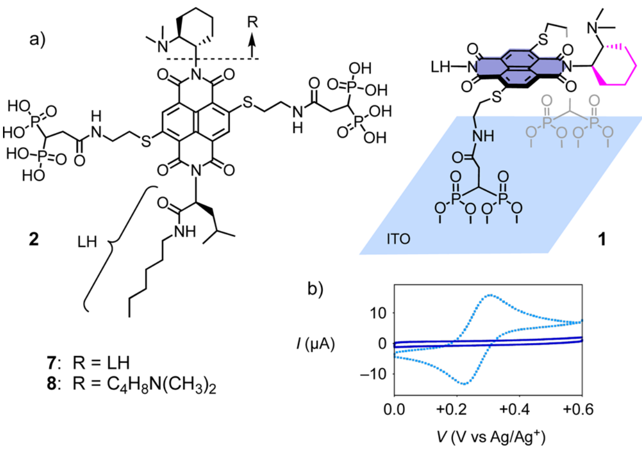

Figure 2. (a) Structure of the electric-field-responsive anion−π catalyst **1**, obtained by immobilization of **2** on ITO. (b) Cyclic voltammograms of aqueous $K_4Fe(CN)_6$ (0.5 mM; 0.2 M Na_2SO_4) measured using an ITO electrode as a working electrode before (dashed) and after (solid) 1 day at 40 °C in a solution of **2** (1 mM) and pyridine (10 mM) in DMSO (counter electrode Pt; reference electrode Ag/AgCl).

working electrodes is completely covered. Covalent bonding of the diphosphonate feet of the catalyst to the oxide surface was achieved by heating the electrode for 1 h at 120 °C. From the NDI reduction wave, a surface coverage $\Gamma = 0.9 \times 10^{-10}$ mol·cm^{-2} was calculated following established procedures (Figure S2b).[18] This surface coverage was consistent with a catalyst that is anchored with both phosphonate groups to the surface (0.5 molecules·nm^{-2}, Figure 2a). Similar flat-lying orientations have been observed previously with various aromatic systems,[19] and they have been applied successfully to template self-organization, stack exchange and self-sorting of multicomponent photosystems.[16,20]

Electric-field assisted anion−π catalysis was examined with the addition of malonic acid half thioester (MAHT) **3** to enolate acceptor **4**. Despite its importance in all, particularly in polyketide biosynthesis,[21] the MAHT addition does not proceed well without enzymes. In the presence of an amine base, MAHT **3** fails to react with enolate acceptors such as **4** to yield the addition product **A** (or **5**) and prefers to decarboxylate into the irrelevant product **D** (or **6**) instead (Figure 3). Often based on tertiary amines, particularly those in cinchona alkaloids, several catalysts have been reported to achieve enolate addition,[22] and related reactions have already been realized on solid surfaces (without electric fields).[23] We have

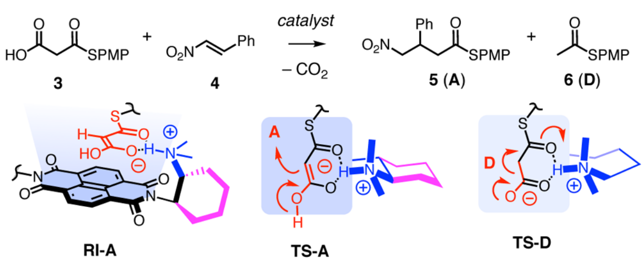

Figure 3. With MAHT **3**, enolate addition to yield product **A** and decarboxylation to product **D** are in kinetic competition. Discrimination between planar (**RI-A**, **TS-A**) and twisted (**TS-D**) tautomers on π-acidic surfaces with tightly (**RI-A**, **TS-A**) but not loosely (**TS-D**) interfaced base catalysts can provide selective access to the disfavored but relevant **A**.

previously shown that the intrinsic selectivity in favor of decarboxylation rather than enolate addition can be reversed using anion−π catalysts.[7,8] Namely, these catalysts are expected to recognize planar enolate tautomers with delocalized negative charge, which undergo addition before decarboxylation (**RI-A**, **TS-A**) rather than decarboxylative deplanarized tautomers with localized charge (**TS-D**).

For electric-field-assisted catalysis, the heterogeneous catalyst **1** was immersed in THF containing 200 mM **3** and 2 M **4**. Hexafluorophosphate (PF_6) salts were used for electrolyte (tetrabutylammonium, $TBAPF_6$, 0.1 M) and reference electrode (Ag/$AgPF_6$) to minimize interference from competing anion−π interactions on the catalyst (see below). The initial velocities v_{ini} of product formation were as low as expected for heterogeneous catalysis (Figure 4b). The ratios of addition

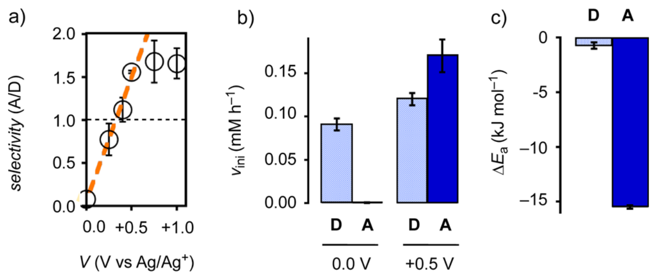

Figure 4. (a) Dependence of A/D product ratio on the potential applied to catalyst **1**. Shown are average values from at least two independent experiments ± error, with linear curve fit for the first four data points. The open circuit potential was 0.040 ± 0.025 V. (b) Initial velocity of the formation of product **D** and **A** in the presence of catalyst **1** at 0.0 V (cyan) and +0.5 V (blue). (c) Transition-state stabilization by +0.5 V for decarboxylation **D** and addition **A** on catalyst **1**, calculated from changes in v_{ini} in panel b.

product **A** and decarboxylation product **D**, that is, the A/D selectivity, were determined by ^{1}H NMR spectroscopy (Figure 4a). At 0 V against Ag/Ag$^+$, A/D = 0.08 was obtained, indicating that decarboxylation to product **6** dominates clearly under these conditions. The effect of negative potentials was not examined because electric-field-induced NDI polarization should weaken rather than strengthen anion−π interactions on the exposed surface (Figure 1) and because of the onset of NDI reduction, that is, catalyst destruction under these conditions. However, the application of increasingly positive potentials caused an almost linear increase in A/D selectivity until saturation was reached around A/D = 1.8 (Figure 4a). This behavior corresponded well to theoretical predictions of the dependence of anion−π interactions on electric fields on the one hand[4] and catalysts operating with binding sites at excess substrate on the other.[6] Linear curve fit of the initial data points gave an apparent field constant n_F = 2.86 V^{-1} for A/D selectivity and an inversion potential of V_I = +0.33 V (Figure 4a).

The inversion of selectivity originated from the selective acceleration of the intrinsically disfavored but relevant enolate addition reaction toward product **A** (or **5**). Comparison of initial rates at 0.0 V and +0.5 V revealed that the application of an electric field to anion−π catalyst **1** results in a rate enhancement of v/v_0 = 190 for the formation of addition product **A** (Figure 4b). In contrast, a nearly negligible rate enhancement of v/v_0 = 1.3 was found for the formation of the decarboxylation product **D** (or **6**) on anion−π catalyst **1** in electric fields (Figure 4b). The different rate enhancements

DOI: 10.1021/jacs.7b02421
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

calculated to transition-state stabilization of $\Delta E_a = -15.5$ kJ mol^{-1} for addition and $\Delta E_a = -0.7$ kJ mol^{-1} for decarboxylation (Figure 4c). Thus, the effect of electric fields on the selectivity of transition-state recognition amounted to $\Delta\Delta E_a = -14.8$ kJ mol^{-1}. This coinciding enhancement of rate and selectivity was in agreement with the fundamental principles of catalysis. Moreover, according to our earlier findings using NDI catalysts of varying π acidity,[8] the selective acceleration of enolate addition was consistent with enhanced anion−π interactions, here caused by the polarization of the π surface in catalyst **1** by electric fields (Figure 1b). Although convincing and consistent, this interpretation does of course not exclude other explanations of the identified remote control of anion−π catalysts in electric fields.

To substantiate electric-field-enhanced anion−π interactions, the effect of the presence of nitrate anions was examined. Due to their recognition on π-acidic surfaces,[2] nitrate anions have been found previously to be effective inhibitors of anion−π catalysts.[7] With heterogeneous catalysis, however, the presence of $TBANO_3$ caused an intrinsic increase in rates and A/D ratios. To extract the impact of electric fields, the change in A/D ratios compared to nearly field-free catalysis, that is, $P_{A/D}$ = A/D/[A/D(0 V)], was determined. With increasing nitrate concentration at +0.5 V, $P_{A/D}$ selectivity decreased with an IC_{50} = 2.2 ± 0.2 mM (Figure 5a). This comparably low IC_{50} was

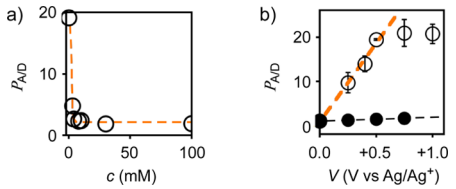

Figure 5. (a) Dependence of $P_{A/D}$ with catalyst **1** at V = +0.5 V on the concentration c of TBA nitrate. The ionic strength was maintained by reducing the concentration of $TBAPF_6$ (100 − c, mM). (b) Dependence of $P_{A/D}$ on the potential applied to catalyst **1** in the absence (○) and the presence (●) of 4.0 mM nitrate, with linear curve fit for the first four data points.

consistent with increasing nitrate−π interactions in response to the polarization of π-acidic NDI surfaces with electric fields (Figure 1b). In the presence of 4.0 mM nitrate, $P_{A/D}$ was nearly independent of electric fields (Figure 5b, ●). Linear curve fit gave a field constant $n_F = 0.9$ V^{-1} for $P_{A/D}$, which was 40 times below the $n_F = 35.7$ V^{-1} for $P_{A/D}$ obtained in the absence of nitrate (Figure 5b, ○). This inhibition by competing nitrate−π interactions provided experimental support that the inversion of selectivity in electric fields originates from electric-field-assisted anion−π interactions.

Control experiments revealed that bare ITO did not catalyze the conversion of MAHT **3**. Also inactive were control catalysts without amine obtained from immobilization of **7** on ITO. In control **8**, the constrained Leonard turn in **2** is replaced by an elongated and flexible *n*-butyl turn between NDI surface and amine catalyst. Immobilized on ITO surfaces, control **8** was inactive. Active but less selective in solution,[8] this finding suggested that the amines on a loose and long chain can reach the solid surface and bind to the oxides. The same amine binding to the oxide surface could have contributed to the inaccessibility of control experiments with simple amine-diphosphonate dyads due to insufficient surface coverage.

In summary, we report that remote control by electric fields can invert the selectivity of anion−π catalysts by selectively accelerating an intrinsically disfavored but relevant enolate addition reaction ("tortoise-and-hare"[7] catalysis). Moreover, we show that the dependence of selectivity on electric fields can be inhibited by nitrate. Although interpretations of results from complex systems always retain their intrinsic speculative component, these results, in agreement with theoretical predictions[4] and all accessible controls, provide strong support for the stabilization of anionic intermediates and transition states on the polarized π surfaces of anion−π catalysts in electric fields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02421.

Detailed experimental procedures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*stefan.matile@unige.ch

ORCID

Stefan Matile: 0000-0002-8537-8349

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NMR and the Sciences Mass Spectrometry (SMS) platforms for services and the University of Geneva, the Swiss National Centre of Competence in Research (NCCR) Molecular Systems Engineering, the NCCR Chemical Biology, and the Swiss NSF for financial support.

■ REFERENCES

(1) (a) Kennedy, C. R.; Lin, S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2016**, *55*, 12596−12624. (b) Dougherty, D. A. *Acc. Chem. Res.* **2013**, *46*, 885−893.

(2) (a) Giese, M.; Albrecht, M.; Rissanen, K. *Chem. Commun.* **2016**, *52*, 1778−1795. (b) Chifotides, H. T.; Dunbar, K. R. *Acc. Chem. Res.* **2013**, *46*, 894−906. (c) Frontera, A.; Gamez, P.; Mascal, M.; Mooibroek, T. J.; Reedijk, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9564−9583. (d) Ballester, P. *Acc. Chem. Res.* **2013**, *46*, 874−884. (e) He, Q.; Ao, Y.-F.; Huang, Z.-T.; Wang, D.-X. *Angew. Chem., Int. Ed.* **2015**, *54*, 11785−11790. (f) Schneebeli, S. T.; Frasconi, M.; Liu, Z.; Wu, Y.; Gardner, D. M.; Strutt, N. L.; Cheng, C.; Carmieli, R.; Wasielewski, M. R.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13100−13104. (g) Watt, M. M.; Zakharov, L. N.; Haley, M. M.; Johnson, D. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 10275−10280. (h) Wang, D.-X.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 892−897. (i) Kobaisi, M. A.; Bhosale, Si. V.; Latham, K.; Raynor, A. M.; Bhosale, Sh. V. *Chem. Rev.* **2016**, *116*, 11685−11796. (j) Liao, J.-Z.; Wu, C.; Wu, X.-Y.; Deng, S.-Q.; Lu, C.-Z. *Chem. Commun.* **2016**, *52*, 7394−7397. (k) Kumar, S.; Ajayakumar, M. R.; Hundal, G.; Mukhopadhyay, P. *J. Am. Chem. Soc.* **2014**, *136*, 12004−12010. (l) Wheeler, S. E.; Houk, K. N. *J. Phys. Chem. A* **2010**, *114*, 8658−8664.

(3) Frontera, A.; Quiñonero, D.; Deyà, P. M. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2011**, *1*, 440−459.

(4) (a) Foroutan-Nejad, C.; Marek, R. *Phys. Chem. Chem. Phys.* **2014**, *16*, 2508−2514. (b) Novák, M.; Foroutan-Nejad, C.; Marek, R. *J. Chem. Theory Comput.* **2016**, *12*, 3788−3795. (c) Farajpour, E.; Sohrabi, B.; Beheshtian, J. *Phys. Chem. Chem. Phys.* **2016**, *18*, 7293−7299.

DOI: 10.1021/jacs.7b02421
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(5) Gorteau, V.; Bollot, G.; Mareda, J.; Perez-Velasco, A.; Matile, S. *J. Am. Chem. Soc.* **2006**, *128*, 14788−14789.
(6) Zhao, Y.; Domoto, Y.; Orentas, E.; Beuchat, C.; Emery, D.; Mareda, J.; Sakai, N.; Matile, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 9940−9943.
(7) (a) Wang, C.; Miros, F. N.; Mareda, J.; Sakai, N.; Matile, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 14422−14426. (b) Cotelle, Y.; Lebrun, V.; Sakai, N.; Ward, T. R.; Matile, S. *ACS Cent. Sci.* **2016**, *2*, 388−393. (c) Liu, L.; Cotelle, Y.; Klehr, J.; Sakai, N.; Ward, T. R.; Matile, S. *Chem. Sci.* **2017**, *8*, 3770−3774.
(8) Cotelle, Y.; Benz, S.; Avestro, A.-J.; Ward, T. R.; Sakai, N.; Matile, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 4275−4279.
(9) Miros, F. N.; Zhao, Y.; Sargsyan, G.; Pupier, M.; Besnard, C.; Beuchat, C.; Mareda, J.; Sakai, N.; Matile, S. *Chem. - Eur. J.* **2016**, *22*, 2648−2657.
(10) (a) Alemani, M.; Peters, M. V.; Hecht, S.; Rieder, K.-H.; Moresco, F.; Grill, L. *J. Am. Chem. Soc.* **2006**, *128*, 14446−14447. (b) Gorin, C. F.; Beh, E. S.; Bui, Q. M.; Dick, G. R.; Kanan, M. W. *J. Am. Chem. Soc.* **2013**, *135*, 11257−11265. (c) Aragonès, A. C.; Haworth, N. L.; Darwish, N.; Ciampi, S.; Bloomfield, N. J.; Wallace, G. G.; Diez-Perez, I.; Coote, M. L. *Nature* **2016**, *531*, 88−91. (d) Shaik, S.; Mandal, D.; Ramanan, R. *Nat. Chem.* **2016**, *8*, 1091−1098. (e) Che, F.; Gray, J. T.; Ha, S.; McEwen, J.-S. *ACS Catal.* **2017**, *7*, 551−562. (f) Gorin, C. F.; Beh, E. S.; Kanan, M. W. *J. Am. Chem. Soc.* **2012**, *134*, 186−189.
(11) (a) Wade, R.; Gabdoulline, R. R.; Lüdemann, S. K.; Lounnas, V. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 5942−5949. (b) Huang, Y. M.; Huber, G.; McCammon, J. A. *Protein Sci.* **2015**, *24*, 1884−1889.
(12) Sakai, N.; Sordé, N.; Matile, S. *J. Am. Chem. Soc.* **2003**, *125*, 7776−7777.
(13) Herrmann, A.; Giuseppone, N.; Lehn, J.-M. *Chem. - Eur. J.* **2009**, *15*, 117−124.
(14) Heaton, R. J.; Peterson, A. W.; Georgiadis, R. M. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 3701−3704.
(15) Chen, C.; Itoh, Y.; Masuda, T.; Shimizu, S.; Zhao, J.; Ma, J.; Nakamura, S.; Okuro, K.; Noguchi, H.; Uosaki, K.; Aida, T. *Science* **2015**, *348*, 555−559.
(16) (a) Sakai, N.; Lista, M.; Kel, O.; Sakurai, S.; Emery, D.; Mareda, J.; Vauthey, E.; Matile, S. *J. Am. Chem. Soc.* **2011**, *133*, 15224−15227. (b) Charbonnaz, P.; Zhao, Y.; Turdean, R.; Lascano, S.; Sakai, N.; Matile, S. *Chem. - Eur. J.* **2014**, *20*, 17143−17151.
(17) See SI.
(18) Bonifazi, D.; Enger, O.; Diederich, F. *Chem. Soc. Rev.* **2007**, *36*, 390−414.
(19) (a) Rochford, J.; Chu, D.; Hagfeldt, A.; Galoppini, E. *J. Am. Chem. Soc.* **2007**, *129*, 4655−4665. (b) Paniagua, S. A.; Hotchkiss, P. J.; Jones, S. C.; Marder, S. R.; Mudalige, A.; Marrikar, F. S.; Pemberton, J. E.; Armstrong, N. R. *J. Phys. Chem. C* **2008**, *112*, 7809−7817.
(20) (a) Orentas, E.; Lista, M.; Lin, N.-T.; Sakai, N.; Matile, S. *Nat. Chem.* **2012**, *4*, 746−750. (b) Hayashi, H.; Sobczuk, A.; Bolag, A.; Sakai, N.; Matile, S. *Chem. Sci.* **2014**, *5*, 4610−4614.
(21) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380−416.
(22) (a) Kobuke, Y.; Yoshida, J. *Tetrahedron Lett.* **1978**, *19*, 367−370. (b) Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841−6844. (c) Pan, Y.; Kee, C. W.; Jiang, Z.; Ma, T.; Zhao, Y.; Yang, Y.; Xue, H.; Tan, C.-H. *Chem. - Eur. J.* **2011**, *17*, 8363−8370. (d) Bew, S. P.; Stephenson, G. R.; Rouden, J.; Godemert, J.; Seylani, H.; Martinez-Lozano, L. A. *Chem. - Eur. J.* **2017**, *23*, 4557−4569.
(23) (a) Puglisi, A.; Annunziata, R.; Benaglia, M.; Cozzi, F.; Gervasini, A.; Bertacche, V.; Sala, M. C. *Adv. Synth. Catal.* **2009**, *351*, 219−229. (b) Motokura, K.; Tada, M.; Iwasawa, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 9230−9235. (c) Zeidan, R. K.; Hwang, S.-J.; Davis, M. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 6332−6335.

DOI: 10.1021/jacs.7b02421
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX