LETTER

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Metal-free oxidation of aromatic carbon–hydrogen bonds through a reverse-rebound mechanism

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Methods for carbon–hydrogen (C–H) bond oxidation have a fundamental role in synthetic organic chemistry, providing functionality that is required in the final target molecule or facilitating subsequent chemical transformations. Several approaches to oxidizing aliphatic C–H bonds have been described, drastically simplifying the synthesis of complex molecules[1–6]. However, the selective oxidation of aromatic C–H bonds under mild conditions, especially in the context of substituted arenes with diverse functional groups, remains a challenge. The direct hydroxylation of arenes was initially achieved through the use of strong Brønsted or Lewis acids to mediate electrophilic aromatic substitution reactions with super-stoichiometric equivalents of oxidants, significantly limiting the scope of the reaction[7]. Because the products of these reactions are more reactive than the starting materials, over-oxidation is frequently a competitive process. Transition-metal-catalysed C–H oxidation of arenes with or without directing groups has been developed, improving on the acid-mediated process; however, precious metals are required[8–13]. Here we demonstrate that phthaloyl peroxide functions as a selective oxidant for the transformation of arenes to phenols under mild conditions. Although the reaction proceeds through a radical mechanism, aromatic C–H bonds are selectively oxidized in preference to activated C_{sp^3}–H bonds. Notably, a wide array of functional groups are compatible with this reaction, and this method is therefore well suited for late-stage transformations of advanced synthetic intermediates. Quantum mechanical calculations indicate that this transformation proceeds through a novel addition–abstraction mechanism, a kind of 'reverse-rebound' mechanism as distinct from the common oxygen-rebound mechanism observed for metal–oxo oxidants. These calculations also identify the origins of the experimentally observed aryl selectivity.

Phthaloyl peroxide (**1**) is a unique molecule because homolysis of the peroxide bond generates a compound possessing two radicals that readily recombine, regenerating the parent peroxide[14]. Although phthaloyl peroxide was first described in the 1950s, there have been few studies examining its reactivity[15–17]. The diradical intermediate generated through homolysis provides opportunities for the development of new reactions, in particular reactions that lead to the oxidative functionalization of C–H bonds.

The reaction of arenes with phthaloyl peroxide was predicted to proceed through three steps: first phthaloyl peroxide (**1**) undergoes a unimolecular reaction to generate diradical **A**[18]; then the combination of one benzoyloxy radical with an arene generates a cyclohexadienyl radical intermediate, **B** (C–O bonding); and lastly the remaining benzoyloxy radical abstracts hydrogen adjacent to the cyclohexadienyl radical (H abstraction) to give phthaloyl ester **C** (Fig. 1). This is a reverse-rebound mechanism to contrast with metal–oxo or dioxirane oxidations involving hydrogen abstraction followed by C–O bonding through oxygen rebound[19,20]. The normal rebound mechanism involving complex **B′** is also shown in Fig. 1, but calculations indicate that it can be ruled out because the energy barrier for the direct abstraction of the aromatic hydrogen is much higher (see Supplementary Information for details and discussion on other pathways).

To test the reactivity of phthaloyl peroxide (**1**) and to evaluate the selectivity of arene versus C_{sp^3}–H functionalization, we conducted initial reactions using 1,3,5-trimethylbenzene (**2a**) (Fig. 2). Preliminary attempts generated 2,4,6-trimethylphenol (**3a**) in 35% yield without evidence of over-oxidation. Optimization of the reaction conditions (Supplementary Information) was achieved through the use of trifluoroethanol or hexafluoroisopropanol as solvent[21], increasing the reaction yields to 78% and 97%, respectively (Fig. 2).

After identifying the optimal conditions, we examined the hydroxylation of a broad range of arenes. For simple and polycyclic arenes (Fig. 3a), the functionalization proceeds smoothly at 23–50 °C in moderate to excellent yields (46%–96%). The transformation can be performed on the multi-gram scale with no need for the exclusion of oxygen and water. In the cases of substrates with different aromatic C–H bonds, the oxidation occurs with selectivity that at first approximation parallels Friedel–Crafts reactivity. In all of the substrates examined, including 1,3,5-triisopropylbenzene (**2i**), the aromatic C–H bond reacts in preference to the benzylic C–H bond.

The products in Fig. 3b, c illustrate the range of functional groups that are tolerated in the aromatic C–H oxidation transformation. Aryl bromides **4a**–**4c** were compatible under the reaction conditions. Anisole derivatives **4d**–**4o** also gave the expected products following reaction with phthaloyl peroxide (**1**). Hydroxylation of biaryl **4i** was selective for the more electron-rich aryl ring and was accomplished without competitive oxidation of the boronate ester. Aryl ketone **4k** and aldehydes **4l**–**4o** also underwent hydroxylation, whereas the use of other oxidants presents a challenge as a result of competing Baeyer–Villiger oxidations. The reactions of **4m** and **4o** cleanly provided products as well, deviating from patterns seen with Friedel–Crafts reactivity. The successful hydroxylation of these substrates led to the systematic examination of functional groups that are inert under

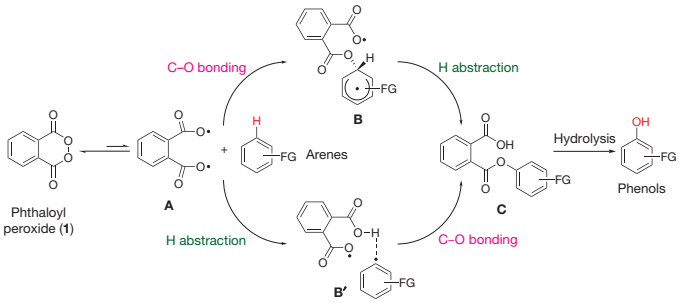

Figure 1 | Proposed diradical activation leading to aryl C–H oxidation through a reverse-rebound mechanism or a rebound mechanism. Two possible modes for the reaction of phthaloyl peroxide (**1**) with arenes: a reverse-rebound mechanism proceeding through a cyclohexadienyl radical (**B**) and a rebound mechanism proceeding through an aryl radical (**B′**). FG, functional group.

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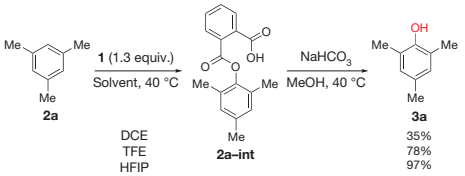

Figure 2 | Reaction of 1,3,5-trimethylbenzene with phthaloyl peroxide (1) and hydrolysis. Abbreviated optimization of the aromatic hydroxylation reaction. See Supplementary Information for additional conditions and peroxides examined. DCE, dichloroethane; HFIP, hexafluoroisopropanol; Me, methyl; TFE, trifluoroethanol.

the reaction conditions, through the use of a series of functionalized vanillate derivatives (Fig. 3c). The reaction conditions were compatible with a wide range of functional groups including alkyl silanes, azides, allenes, nitriles, alkyl boronates and epoxides. Notably, the allyl ether **6k** reacted selectively at the arene despite the known reaction of phthaloyl peroxide with alkenes[15–17] and the highly activated methylene of the allylic ether.

This transformation is amenable to late-stage oxidative functionalization of intermediates in the synthesis of complex molecules for biological evaluation. One example is the natural product (+)-δ-tocopherol, which decreases the incidence of prostate cancer as demonstrated in a 2003 clinical trail[22]. The oxidation of dehydroxy-(+)-δ-tocopherol **8** with phthaloyl peroxide (**1**) delivered tocopherol **9** and isomers in 47% yield (Fig. 4a). Treatment of triflate **10** at 23 °C with peroxide **1** produced phenol **11** in 54% yield (this reaction was also conducted on the 12-g scale in 45% yield). With the triflate functioning as an excellent synthetic handle for coupling reactions, the study of the (+)-δ-tocopherol derivatives can be easily pursued. Dehydroabietylamine derivatives have been shown to have important biological effects including the reduction of inflammatory responses, and potentially function as a phospholipase-A_2 inhibitor[23]. The hydroxylation of the dehydroabietylamine derivative **12** with phthaloyl peroxide (**1**) provided phenol **13** in 63% yield, comparing well with the existing method for introducing phenolic functionality[24] (Fig. 4b). A direct comparison illustrates how the phthaloyl peroxide process circumvents Friedel–Crafts/Baeyer–Villiger sequences, improving on the step economy[25]. (Step economy considerations minimize the number of synthetic steps required to access a targeted compound, improving the efficiency and, in turn, generating material in an expedited manner.) A derivative of the natural product clovanemagnolol was selected owing to its importance in regenerative

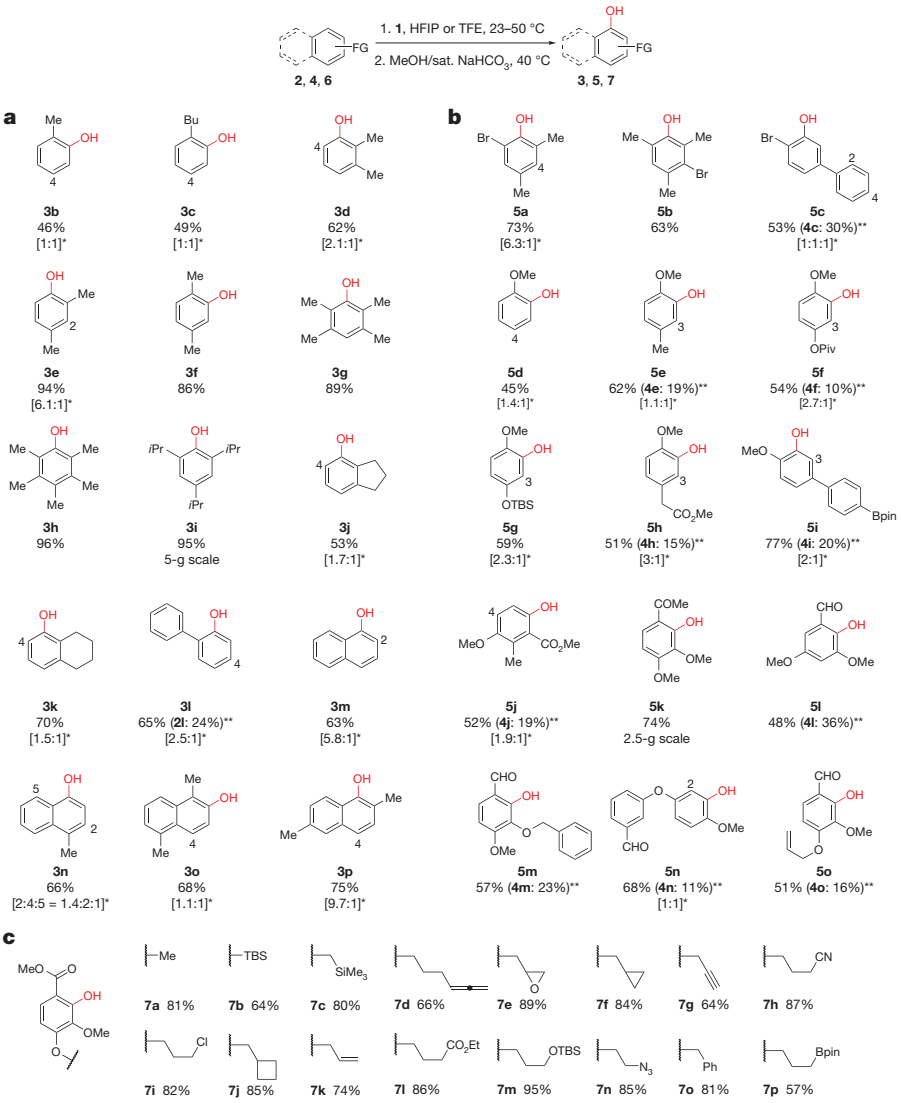

Figure 3 | Phthaloyl peroxide (1)-mediated hydroxylation of arenes. **a**, Hydroxylation of simple and polycyclic arenes. **b**, Hydroxylation of functionalized arenes. **c**, Functional group compatibility test: hydroxylation of methyl vanillate derivatives. Isolated yields are indicated below each entry. See Supplementary Information for experimental details. Bpin, pinacol boronate; Et, ethyl; *i*Pr, $CH(CH_3)_2$; Piv, pivaloyl; TBS, *tert*-butyldimethylsilyl. *The minor regioisomeric position is labelled with the corresponding carbon atom number. **The yield in parentheses refers to the starting material recovered.

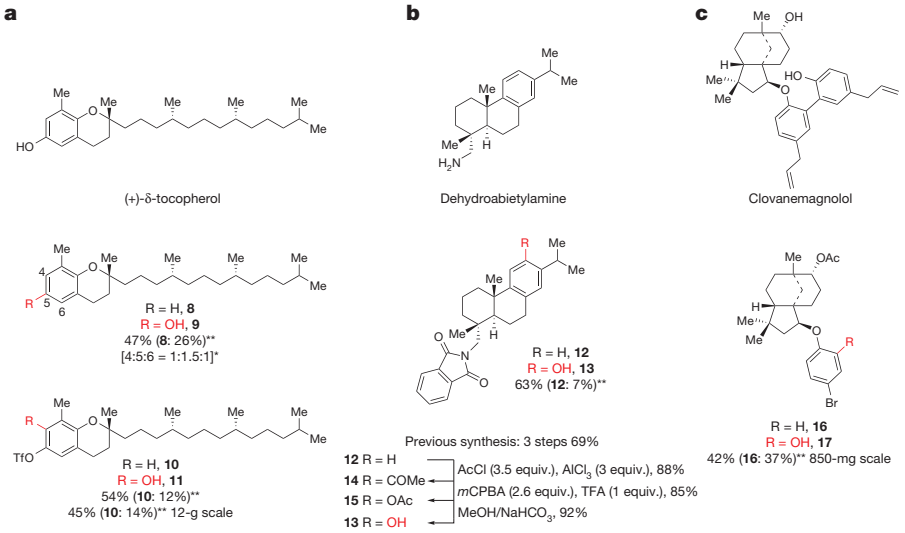

Figure 4 | Hydroxylation of (+)-δ-tocopherol, dehydroabietylamine and clovanemagnolol derivatives. **a**, Preparation of (+)-δ-tocopherol and its derivatives. **b**, Comparison of the synthesis of dehydroabietylamine derivative **13** using a standard Friedel–Crafts/Baeyer–Villiger sequence. **c**, Functionalization of the clovanemagnolol precursor **16**. Isolated yields are indicated below each entry. See Supplementary Information for experimental details. Ac, acetyl; *m*CPBA, *meta*-chloroperoxybenzoic acid; Tf, trifluoromethanesulphonate; TFA, trifluoroacetic acid. *The minor regioisomeric position is labelled with the corresponding carbon atom number. **The yield in parentheses refers to the starting material recovered.

science. Following synthesis as in ref. 26, bromide **16** was prepared and subjected to oxidation mediated by phthaloyl peroxide (**1**) to give the hydroxylated product **17** cleanly (Fig. 4c).

On the basis of quantum mechanical calculations[27], this metal-free aromatic C–H oxidation is most likely to occur through a reverse-rebound diradical mechanism (via intermediate **B**; Fig. 1). Extensive tests of various density functional theory and *ab initio* methods for the chemical system investigated are given in Supplementary Information. Previous tests have also established that the (U)B3LYP/6-31+G(d) methodology, used to produce the results in Figs 5 and 6, provides a good compromise between accuracy and efficiency, and has given good results for peroxide energetics[28]. The free-energy surfaces for reactions of the aromatic and benzylic C–H bonds of mesitylene (**2a**) by diradical **A** from phthaloyl peroxide or benzoyloxy radical **D** are shown in Fig. 5. As illustrated in Fig. 5a, the addition of one radical centre in **A** (Fig. 6a) to the aromatic ring of mesitylene requires a free energy of only 10.0 kcal mol^{-1}. The subsequent intramolecular hydrogen transfer[29] in intermediate **B** is very easy, with a barrier of less than 4 kcal mol^{-1}. The structures involved in these processes are shown in Fig. 6b, c. Therefore, the radical addition step is rate determining in the

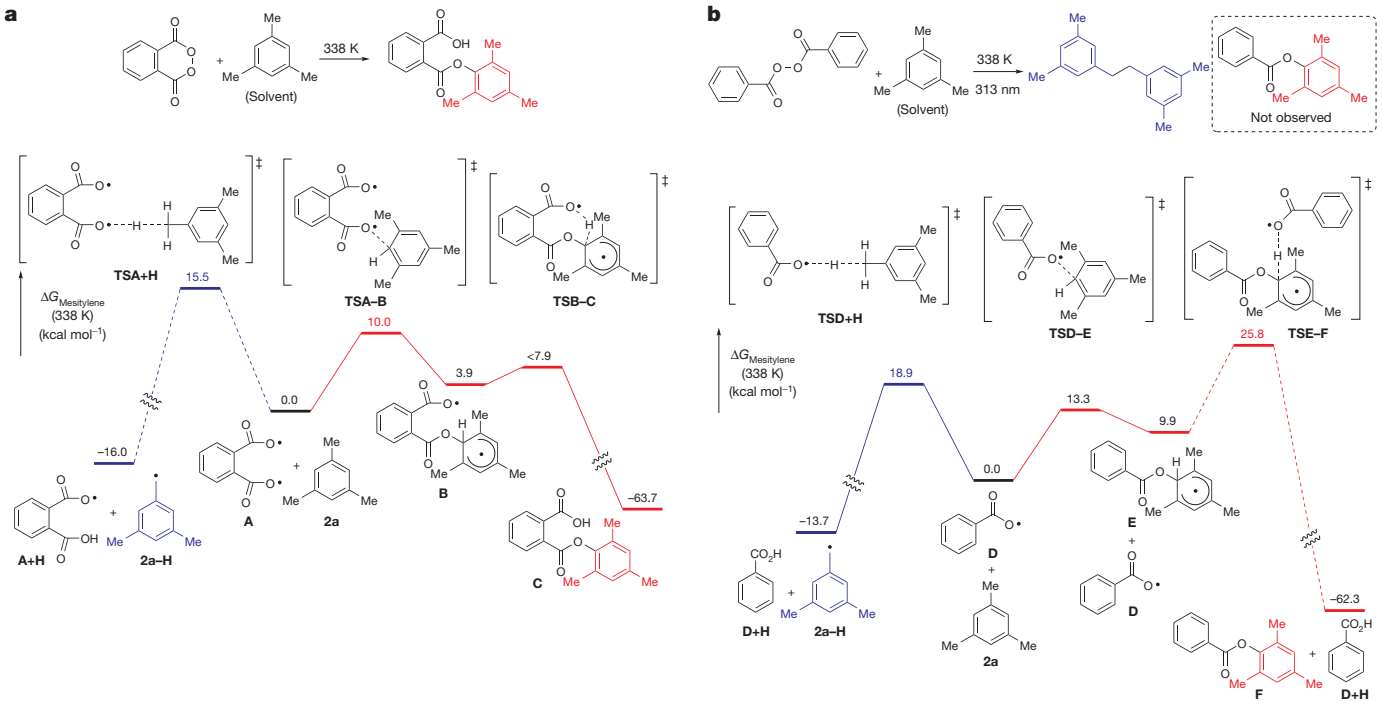

Figure 5 | Experimental results and computed free-energy surfaces for the functionalization of aromatic and benzylic C–H bonds of mesitylene. **a**, Reaction pathways involving diradical **A** generated from the thermal decomposition of phthaloyl peroxide. **b**, Reaction pathways involving benzoyloxy radical **D** generated from benzoyl peroxide under irradiation with 313-nm light. Free energies in mesitylene computed using the (U)B3LYP/6-31+G(d) methodology with the CPCM solvation correction. CPCM, conductor-like polarizable continuum model; TS, transition state.

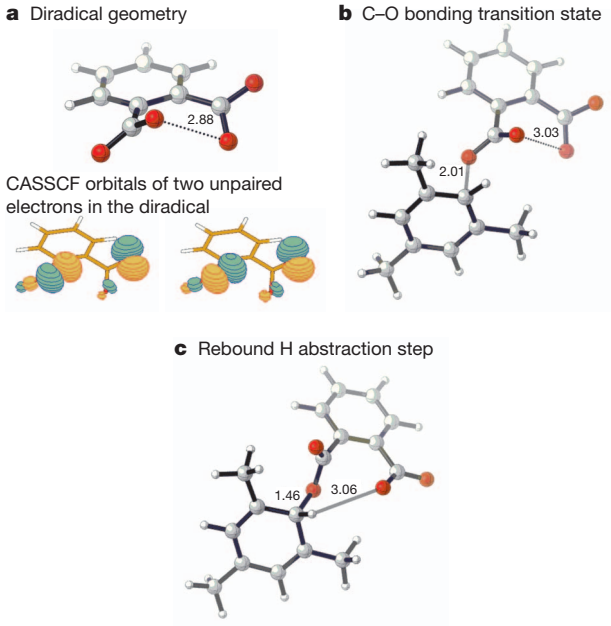

Figure 6 | Structures involved in the reverse-rebound mechanism. **a**, Diradical geometry and singly occupied orbitals. CASSCF, complete active space self-consistent field. **b**, Carbon–oxygen bonding transition state. **c**, Rebound hydrogen abstraction step. Distances are given in ängströms.

diradical-mediated aromatic C–H oxidation. The direct hydrogen abstraction to form benzylic radical **2a−H** is disfavoured; the corresponding barrier is 5.5 kcal mol^{-1} higher than for the aromatic C–H functionalization (Fig. 5a). This difference accounts for the aryl selectivity under the experimental conditions. By contrast, benzoyloxy radical **D**, formed from benzoyl peroxide, reacts with mesitylene (**2a**) to give only the benzylic C–H-functionalized product under similar conditions[30] (Fig. 5b). The computed activation free energy of the benzylic hydrogen abstraction by benzoyloxy radical **D** is 18.9 kcal mol^{-1}. In this case, the two-step aromatic C–H functionalization is disfavoured; the intermolecular hydrogen abstraction by **D** from radical intermediate **E** becomes rate determining with a much higher overall barrier of 25.8 kcal mol^{-1} (Fig. 5b). This is in agreement with the experimental fact that benzoyloxy-radical-mediated aromatic C–H oxidation is not observed.

Although diradical **A** is predicted to be somewhat more reactive than radical **D**, both can be added to the aromatic ring of **2a** more easily than a benzylic hydrogen can be abstracted. With radical **D** from benzoyl peroxide, the subsequent bimolecular hydrogen abstraction from intermediate **E** has a high barrier, and the reversion to **D** and **2a** followed by benzylic hydrogen abstraction is favoured. With diradical **A** from phthaloyl peroxide, the addition to the aromatic ring is followed by an instantaneous intramolecular hydrogen abstraction; the efficient reverse-rebound mechanism occurs, leading to highly selective aromatic C–H oxidation.

The phthaloyl peroxide (**1**)-mediated hydroxylation of arenes provides a new, selective method for the conversions of arenes to phenols. The hydroxylation procedure is performed under mild conditions without the use of metallic reagents or strong acids, saving time, cost and purification steps. Moreover, this methodology possesses broad functional group compatibility, has excellent selectivity for aromatic C–H bonds and does not lead to over-oxidation. The tolerance of the reaction towards a variety of functional groups permits the modification of advanced synthetic intermediates. Mechanistic insights into the reverse-rebound process provide a novel strategy for selective C–H functionalization and lay the foundation for the discovery of new chemical transformations using diradicals.

METHODS SUMMARY

General procedure for the hydroxylation of arenes. A borosilicate flask was equipped with a magnetic stir bar, and neat or solid arene (0.2–0.8 mmol) was added. Addition of hexafluoroisopropanol or trifluoroethanol (2–5 ml) to provide a 0.2 M solution was followed by the addition of solid phthaloyl peroxide (**1**, 1.3 equiv.) in portions over 90 s. The reaction flask was placed in a heated oil bath (23–50 °C). After 3–24 h, the flask was removed from the oil bath and cooled to ambient temperature (23 °C). The reaction was then concentrated, and under positive N_2 pressure (to avoid potential air oxidation of the phenolic product) MeOH (3 ml) and saturated aqueous $NaHCO_3$ solution (0.2 ml) were added and the solution was stirred. After 12 h, the reaction was quenched with phosphate buffer (5 ml, pH 7.0) and extracted with EtOAc (10 ml × 3), and the combined organic layers were washed with brine (5 ml), dried over Na_2SO_4 and concentrated. The crude material was purified by silica-gel column chromatography to afford the desired phenolic product. For full experimental details and characterization of new compounds, see Supplementary Information.

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Supplementary Information is available in the online version of the paper.

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Author Contributions C.Y. designed experiments; C.Y., T.H. and A.B. carried out experiments; Y.L. and K.N.H. carried out computational analyses; C.Y., Y.L., K.N.H. and D.S. analysed data; K.N.H. and D.S. supervised research; C.Y., Y.L., K.N.H. and D.S. wrote the paper.

Author Information Supplementary crystallographic data for compound **2a–int** have been deposited at the Cambridge Crystallographic Data Centre under accession number CCDC 903297. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/data_request/cif. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to D.S. (dsiegel@cm.utexas.edu).