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Remote *Meta*-C−H Activation Using a Pyridine-Based Template: Achieving Site-Selectivity via the Recognition of Distance and Geometry

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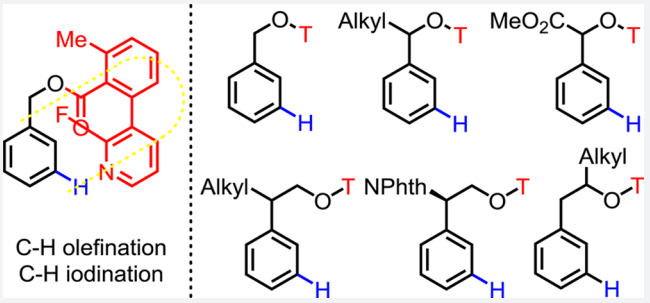
Supporting Information

ABSTRACT: The pyridyl group has been extensively employed to direct transition-metal-catalyzed C−H activation reactions in the past half-century. The typical cyclic transition states involved in these cyclometalation processes have only enabled the activation of *ortho*-C−H bonds. Here, we report that pyridine is adapted to direct *meta*-C−H activation of benzyl and phenyl ethyl alcohols through engineering the distance and geometry of a directing template. This template takes advantage of a stronger σ-coordinating pyridine to recruit Pd catalysts to the desired site for functionalization. The U-shaped structure accommodates the otherwise highly strained cyclophane-like transition state. This development illustrates the potential of achieving site selectivity in C−H activation via the recognition of distal and geometric relationship between existing functional groups and multiple C−H bonds in organic molecules.



INTRODUCTION

σ-Chelation is among the most powerful tools in developing transition-metal-catalyzed reactions including epoxidation,[1] hydrogenation,[2,3] and hydroformylation[4,5] of double bonds. The importance of the directing effect has greatly elevated in the development of selective C−H metalation reactions due to the presence of multiple C−H bonds in substrates.[6−10] One of the most significant challenges in the field of C−H activation is the differentiation of multiple C−H bonds in a given organic molecule due to a lack of parameters for recognition. We envisioned that the distal and geometrical relationship between the existing functional group and different C−H bonds at various locations can be potentially discerned and recognized to achieve site selectivity by using preinstalled templates that adopt conformations which prefer C−H activation transition states that are distal rather than proximal to a given functional group. However, current directing groups, such as the well explored pyridyl moiety, can only direct the activation of C−H bonds that are close in distance and geometrically accessible, typically *ortho*-C−H bonds due to the chelating effect.[11−20] Such constraint has prevented functionalization of the majority of C−H bonds in organic substrates, thus limiting the application of C−H activation reactions in synthesis (Figure 1a). Although *meta*-C−H functionalizations are also possible through recognizing steric or electronic effects of substrates,[21−24] development of directed *meta*-C−H functionalizations is important and complementary when substrates do not have such intrinsic bias. Recently, *meta*-selective C−H functionalization of 2-phenylpryidines has been demonstrated via a directed *ortho*-metalation which then triggers subsequent S_EAr-type substitution at the *meta*-position.[25−30] To achieve directed *meta*-metalation, we and others developed a number of U-shaped nitrile templates that can direct remote *meta*-C−H activation through a macro-cyclophane-like transition state.[31−40] Encouraged by these developments, we envisioned that, by engineering the distance and geometry of the template to accommodate a macrocyclic cyclophane-like pretransition state, the strong coordinating pyridyl group could be adapted to direct remote *meta*-C−H metalation (Figure 1b). Here, we report the development and evaluation of pyridine-based templates that direct *meta*-C−H functionalizations of alcohols. The development of *meta*-iodination reaction has not been successful using previous nitrile-based templates. The strongly coordinating pyridyl group is beneficial for recruiting Pd(II) catalysts in the presence of other coordinating reagents. On the other hand, the macrocyclic palladacycle intermediate is destabilized by the cyclophane strain to afford high reactivity for subsequent functionalization. The ester linkage also renders the removal of the template operationally simple for late-stage

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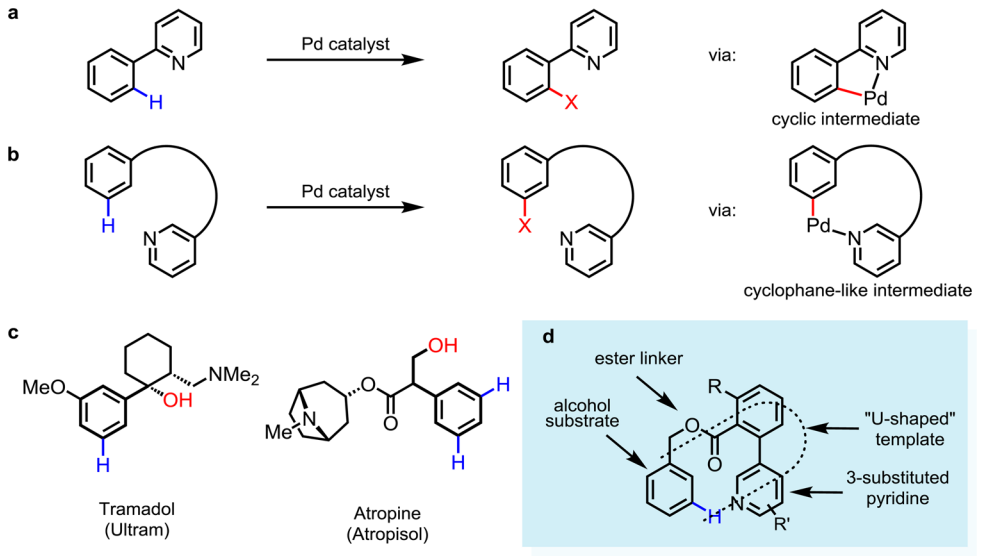

Figure 1. Design of new template for *meta*-C−H activation. (a) Pyridyl group directs *ortho*-C−H activation via cyclic intermediate. (b) Pyridyl group directs *meta*-C−H activation via cyclophane-like intermediate. (c) Structurally related drug molecules (brand names in parentheses). (d) Key features in the newly designed template.

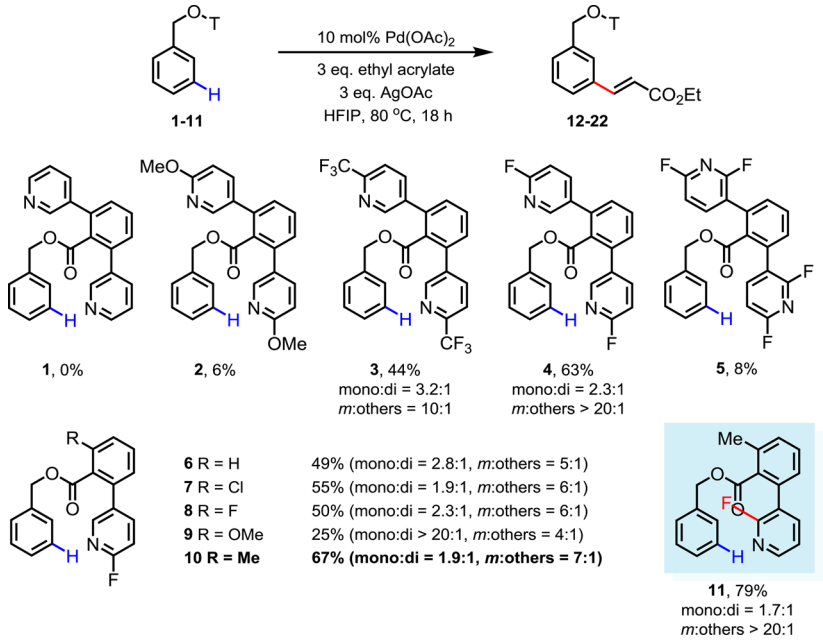

Figure 2. Tuning of pyridine-based template.

modification of bioactive molecules. In light of the synthetic utility and biological importance of alcohols (Figure 1c), this *meta*-C−H functionalization method could prove broadly useful.

RESULTS AND DISCUSSION

The key design principles of our previous nitrile-based template for *meta*-C−H activation are two-fold.[31] First, the substrate adopts a U-shaped conformation so that the coordinating group reaches the remote C−H bonds; second, the linear nitrile coordinates Pd through an end-on coordination mode thereby favoring the *meta*-C−H activation over *ortho*-C−H activation by reducing the strain of the cyclophane-like transition states. The intrinsic shortcoming of this template is that the weakly coordinating nitrile group may not coordinate with Pd(II) effectively in the presence of other coordinating reagents or solvents, thus greatly limiting the scope of substrates and transformations. We wondered whether we could replace nitrile by a stronger coordinating group, while maintaining the U-shaped conformation as well as mimicking the end-on coordination so that Pd(II) could be recruited more effectively to the *meta*-position. This preliminary rationale has led us to synthesize various pyridine-based templates in which the nitrogen is placed at the *meta*-position in relation to where the substrates are attached. In this molecular design, the direction of the lone pair toward the *meta*-C−H bonds can best mimic that of the nitrile (Figure 1d). Thus, benzyl alcohol is attached to various pyridine templates via a readily removable ester linkage.

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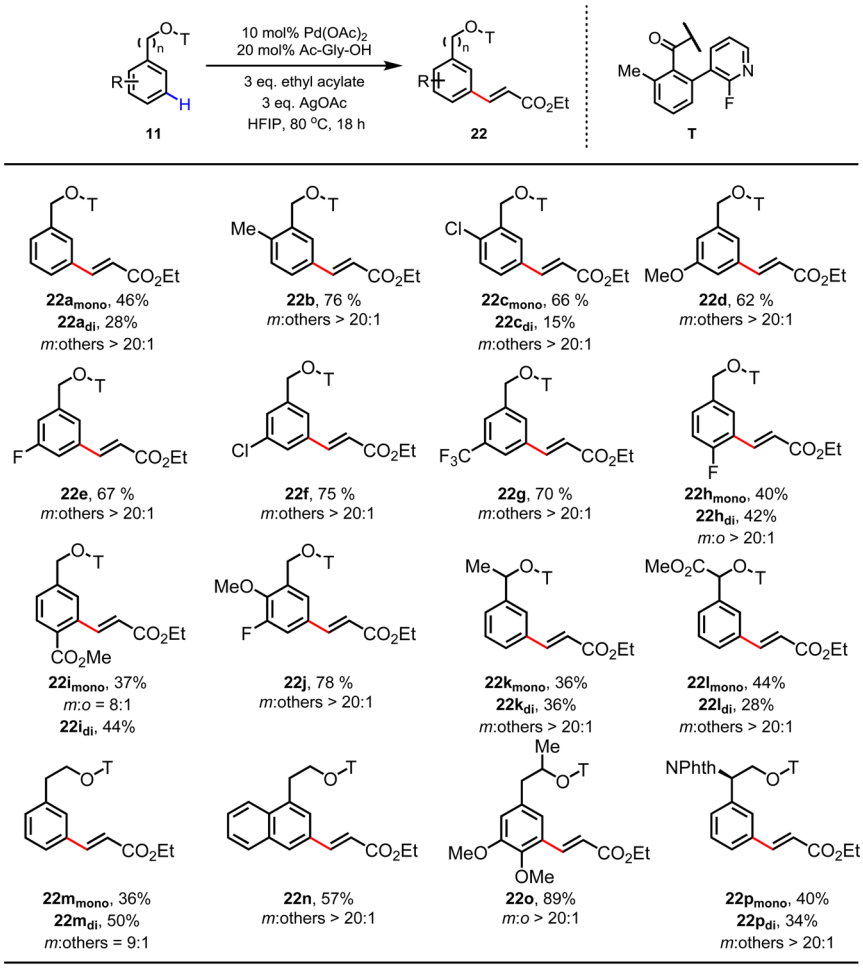
Table 1. *Meta*-C−H Olefination of Alcohols[a]



[a]Isolated yields. Selectivity was determined by GC-MS.

The simple pyridyl moiety in substrate **1** is subjected to various previously developed *meta*-C−H olefination conditions, and no olefination product could be detected. It is possible that two pyridines from two substrate molecules could coordinate with Pd(II) to form an unreactive complex (Figure 2). Introducing a methoxy group at the C-2 position of the pyridyl in substrate **2** to tune the coordinating power of the pyridyl group leads to the formation of an olefinated product in 6% yield. Encouragingly, the C−H olefination occurs exclusively at the *meta*-position, validating our design principle. Thus, we introduced various substitutions onto the C-2 position of the pyridine ring to modulate the coordination and discovered that electron-withdrawing trifluoromethyl and fluoro groups at the C-2 position improved the yields of the olefinated products to 44 and 63% respectively. The *meta*-selectivity with substrate **4** also reaches >20:1. Template containing 2,6-difluoropyridyl is not effective (**5**). To simplify the template, we prepared variously substituted templates **6**−**10** containing a single pyridine ring. Replacement of one of the pyridyl groups by hydrogen, chloro, fluoro, and methoxy groups reduced both yields and selectivity significantly (**6**−**9**). The presence of a methyl in place of the pyridyl, however, restored the reactivity affording olefinated products in 67% yield with moderate *meta*-selectivity (**10**, *meta*:others = 7:1). This improved reactivity could be attributed to a conformational restriction exerted by the methyl group which helps position the aryl ring in proximity to the pyridyl group. To our surprise, switching 2-fluoro-5-pyridyl group (**10**) to 2-fluoro-3-pyridyl group (**11**) improved both yield and *meta*-selectivity significantly (**11**, 79% yield, *meta*:others >20:1).

The established template is then attached to a variety of benzyl and phenylethyl alcohols to test *meta*-C−H olefination. Although the influence of mono-*N*-protected amino acid ligand on the olefination of substrates **11a**, **11b**, **11c**, **11d**, and **11h** is minor, the use of Ac-glycine improves the yield by 10−20% with other substrates (Table 1). Nonsubstituted benzyl alcohol gives a mixture of mono- and di-*meta*-olefination products in 74% isolated yield (**22a**$_{mono}$, 46%, **22a**$_{di}$, 28%). *Ortho*-substituted benzyl alcohols give mainly the mono-*meta*-olefinated product at the less hindered position in moderate to good yields (**22b**, **22c**). *Meta*-substituted benzyl alcohols give the *meta*-olefination products in good yields (**22d**-**22g**). Regardless of the electronic nature of the substituents, excellent *meta*-selectivity is obtained. *Para*-fluoro and methoxycarbonyl groups are well tolerated affording mono- and di-*meta*-olefination products in good yields (**22h**, **22i**). An *ortho*,*meta*-disubstituted benzyl alcohol is also successfully olefinated in good yield and *meta*-selectivity (**22j**). Olefination of secondary benzyl alcohols **11k** and **11l** provide similar results to that of **11a**. Gratifyingly, the same template can also effectively direct *meta*-C−H olefination of phenylethyl alcohols demonstrating great flexibility of this template (**22m**−**22p**).

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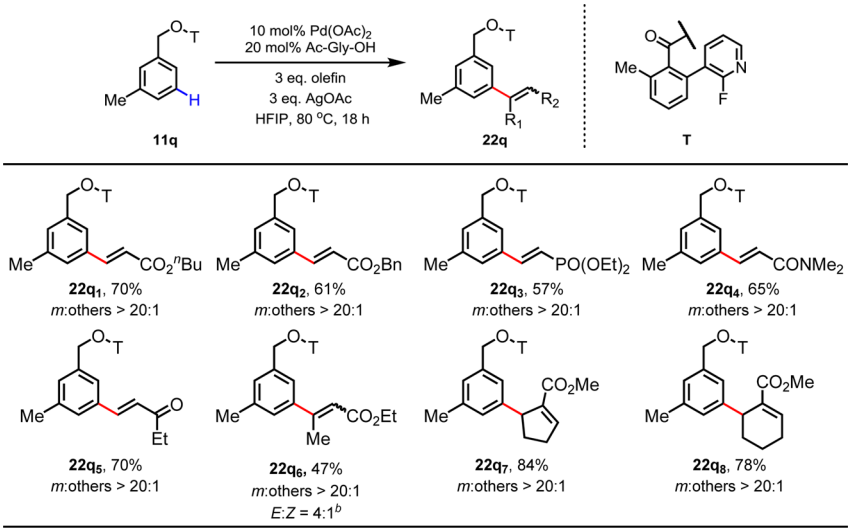
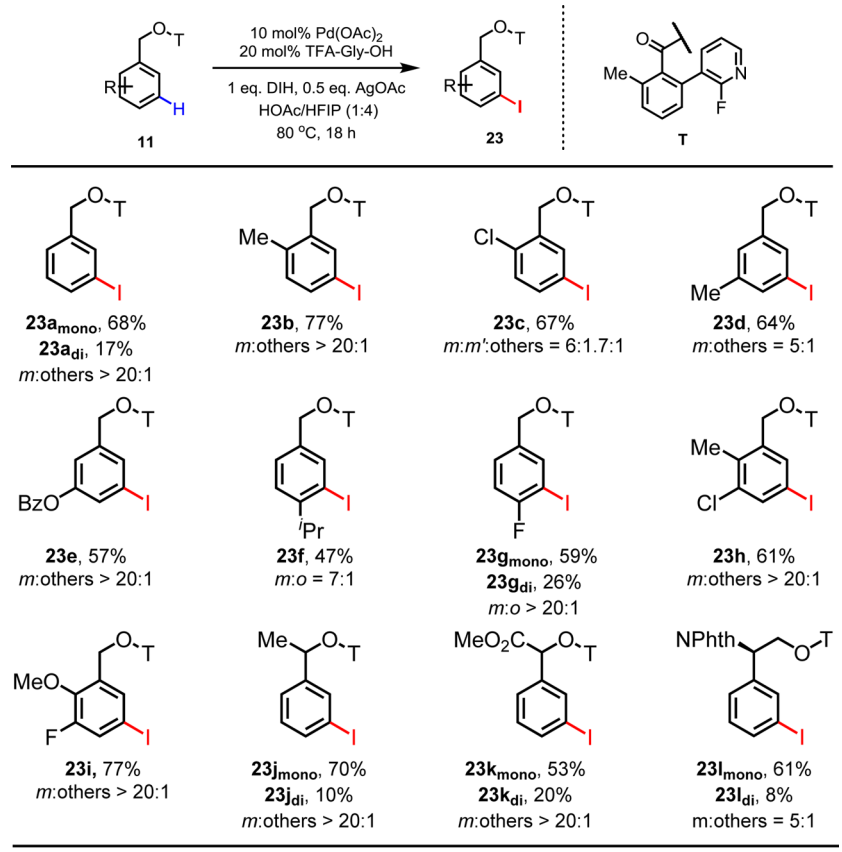
Table 2. Scope of Olefin Coupling Partners[a]



[a]Isolated yields. Selectivity was determined by GC-MS.[b]Determined by ^{1}H-NMR spectroscopy.

Table 3. *Meta*-C−H Iodination of Alcohols[a]



[a]Isolated yields. Selectivity was determined by GC-MS. DIH = 1,3-diiodo-5,5-dimethylhydantoin.

Next, we examined the scope of olefin coupling partners (Table 2). α,β-Unsaturated ester, phosphonate, amide, and ketone ($\mathbf{22q_1}$−$\mathbf{22q_5}$) are reactive, affording the desired product in good yields. This reaction is also compatible with olefins containing α,β-substituents, albeit affording lower yield ($\mathbf{22q_6}$). Cyclic α,β-unsaturated esters give excellent yields ($\mathbf{20q_7}$, $\mathbf{20q_8}$). In all cases, high levels of *meta*-selectivity are observed (*meta*:others >20:1).

Having established the feasibility of using 3-pyridyl motif to direct *meta*-C−H olefination, we sought to apply this new template to other *meta*-C−H activation transformations that are not compatible with our previous nitrile-based templates. Considering the lack of diverse *meta*-C−H functionalization transformations, *meta*-C−H iodination could provide a stepping stone toward the desired functional groups as aryl iodide intermediates are amenable to a wide range of transformations, especially transition-metal-catalyzed carbon−

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carbon and carbon−heteroatom bond forming reactions.[41−44] So far, the widely used directed lithiation/iodination can only introduce the iodide onto the *ortho*-position.[6] Recently, an elegant example of *meta*-C−H halogenations via directed *ortho*-metalation and subsequent S_EAr-type bromination[28] has been reported. We subjected model substrate **11a** to a wide range of previously known C−H iodination conditions, and found that 1,3-diiodo-5,5-dimethylhydantoin (DIH) is reactive for *meta*-C−H iodination, affording the *meta*-iodinated product in 21% yield (see Table S1). Addition of acetic acid improved the yield to 51%, presumably through helping the regeneration of the Pd(II) catalyst.[45] Among the mono-*N*-protected amino acid ligands (MPAA) previously used to promote C−H activation reactions, *N*-trifluoromethylacetyl glycine was found to be the optimal ligand for this reaction, affording **23a** in 62% yield (Table S2). A substoichiometric amount of silver acetate was added to scavenge the iodide from Pd−I species to increase the turnover numbers, improving the yield to 85% (Table S3). Extending this halogenation protocol to bromination and chlorination using NBS and NCS gave low yields under current conditions (20−30%).

The scope of this *meta*-C−H iodination protocol is also investigated (Table 3). A variety of *ortho*-, *meta*-, and *para*-substituted benzyl alcohols are compatible (**23a**−**g**). Methyl, fluoro, and chloro substitution give the *meta*-iodinated products in 64−85% yields with good to excellent *meta*-selectivity (**23b**−**d**,**g**). *Meta*-benzoyl protected phenol substrate **23e** is also iodinated at the *meta*-position in excellent *meta*-selectivity, without being influenced by the electron-donating benzoxyl group. *Meta*-selectivity is also achieved in the presence of a sterically hindered *para*-isopropyl group (**23f**). Disubstituted benzyl alcohols give excellent *meta*-selectivity in general (**23h**, **23i**). The versatility of this reaction is also demonstrated by the *meta*-selective iodination of secondary benzyl alcohols (**23j** and **23k**) and 2-phenylglycinol (**23l**). Finally, the template was removed via hydrolysis under basic conditions in high yield to give *meta*-iodinated free benzyl alcohols (Figure 3).

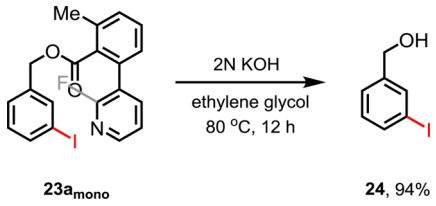

Figure 3. Removal of the directing template.

CONCLUSION

In conclusion, we have demonstrated that conventional strongly coordinating *ortho*-directing groups such as pyridyl groups can be engineered to direct remote *meta*-C−H activation through molecular design based on distance and geometry. The advantage of this new class of *meta*-directing groups is evident from the newly developed *meta*-C−H iodination reaction that is not compatible with our previous nitrile template.

METHODS

General Procedure for Template-Directed *Meta*-C−H Olefination of Alcohols. A 10 mL sealed tube was charged with substrate (0.2 mmol, 1.0 equiv), olefin (3.0 equiv), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol %), AgOAc (3.0 equiv), and HFIP (2 mL). The tube was then sealed and submerged into a preheated 80 °C oil bath. The reaction mixture was stirred at 80 °C for 18 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to give the desired product. The positional selectivity was determined by GC−MS with a flame ionization detector.

General Procedure for Template-Directed *Meta*-C−H Iodination of Alcohols. A 10 mL sealed tube was charged with substrate (0.2 mmol, 1.0 equiv), DIH (1.0 equiv), $Pd(OAc)_2$ (10 mol %), TFA-Gly-OH (20 mol %), AgOAc (0.5 equiv), HOAc (0.4 mL), and HFIP (1.6 mL). The tube was then sealed and submerged into a preheated 80 °C oil bath. The reaction mixture was stirred at 80 °C for 18 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative LC−MS to give the desired product. The positional selectivity was determined by GC−MS with a flame ionization detector.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.5b00312.

Experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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