Buchwald–Hartwig Amination and C–S/S–H Metathesis of Aryl Sulfides by Selective C–S Cleavage Mediated by Air- and Moisture-Stable [Pd(NHC)(μ-Cl)Cl]$_2$ Precatalysts: Unified Mechanism for Activation of Inert C–S Bonds

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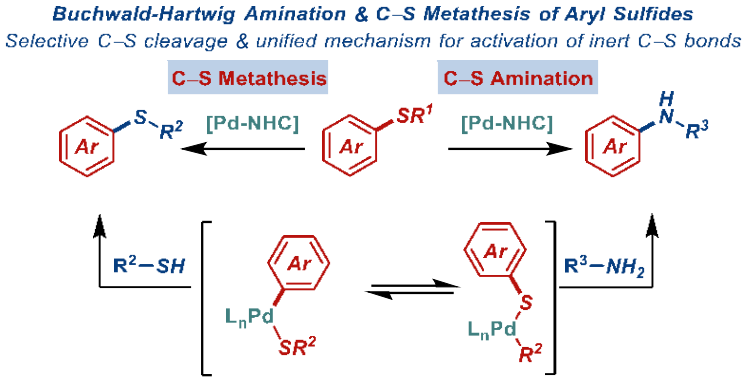
Supporting Information



ABSTRACT: We report a combined experimental and mechanistic study on the Buchwald–Hartwig amination and C–S/S–H metathesis of aryl sulfides by selective activation of C–S bonds mediated by well-defined, air- and moisture-stable Pd(II)–NHC precatalysts, [Pd(NHC)(μ-Cl)Cl]$_2$. This class of Pd(II)–NHC precatalysts displays excellent activity in the cross-coupling of aryl sulfides. Most crucially, we unravel the unified mechanism for activation of C–S bonds in the C–N cross-coupling and C–S metathesis manifolds, where the inert C–S bond serves as a precursor to valuable amine or thioether products.

Transition-metal-catalyzed cross-couplings have had a tremendous impact on organic synthesis and catalysis in the past decades.[1-4] The transformative effect of cross-coupling reactions is highlighted by the abundance of daily applications in the fields ranging from fine chemical synthesis, polymers and functional materials to medicinal chemistry and drug discovery.[3] The predictable nature of palladium-catalyzed cross-couplings, with well-defined two electron catalytic cycles and well-characterized reactivity trends, has presented an immense opportunity for organic chemists to incorporate cross-couplings as an indispensable tool in synthetic planning and this impact was recognized by the 2010 Nobel Prize in Chemistry.[4]

However, despite major developments in cross-coupling of halides and pseudohalides, the cross-coupling of inert bonds remains underdeveloped (Figure 1A).[5-9] The comparative scarcity of efficient and modular methods for the catalytic cross-coupling of inert bonds is particularly striking considering that (1) many functional groups are inherently present in late-stage intermediates; thus their activation may facilitate the development of more active therapeutics and compound libraries for activity screening; (2) many bonds are as readily accessed from chemical feedstocks as aryl halides and pseudohalides; (3) the capacity to predictably activate inert bonds may be exploited in highly valuable orthogonal couplings owing to different bond dissociation energies that determine the rate of oxidative addition in well-defined catalytic cycles. New mechanistic insights that generalize coupling manifolds are essential to provide pathways for broad applications across substrates classes.[5-9]

In this context, aryl sulfides represent a highly attractive class of inert bond electrophiles owing to the privileged role of sulfur in medicinal chemistry.[10] Recent progress notwithstanding, the cross-coupling of aryl sulfides by

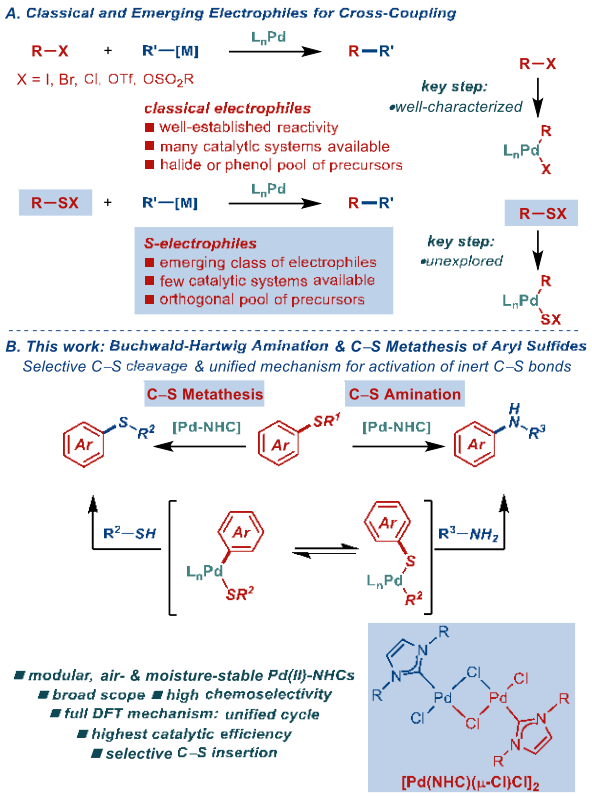


Figure 1. (a) Cross-coupling of classical and C–S electrophiles; (b) Buchwald-Hartwig amination and C–S metathesis of aryl sulfides: unified mechanism for C–S activation.

palladium catalysis is severely underdeveloped, despite the obvious benefits that this activation may offer,[11] and with the advantage that in certain cases C-S bonds are more reactive than C-N and C-O bonds.[11] It is worth noting that C-S bonds are significantly more difficult to activate through oxidative addition than aryl chlorides.[11,12] In continuation of our studies on catalyst development, we were intrigued to leverage potential of well-defined, air- and moisture-stable Pd(II)–NHC chloro dimers, [Pd(NHC)(μ-Cl)Cl]$_2$, as a general class of catalysts for C–S bond activation.[13] In particular, the straightforward, one-step synthesis, high bench-stability, operational-simplicity, fast activation and superior atom-economic profile of Pd(II)–NHC chloro dimers render these catalysts a privileged class in the arsenal of Pd catalysts for cross-coupling reactions, while (1) benefiting from strong electronic σ-donation and umbrella-type steric arrangement of NHC ligands that are distinct from tertiary phosphines; and (2) avoiding problems associated with palladacycle, allyl and heterocycle-type throw-away ligands in catalyst activation to monoligated Pd(0) in well-defined and air-stable Pd(II)–NHC catalysis.[12,13]

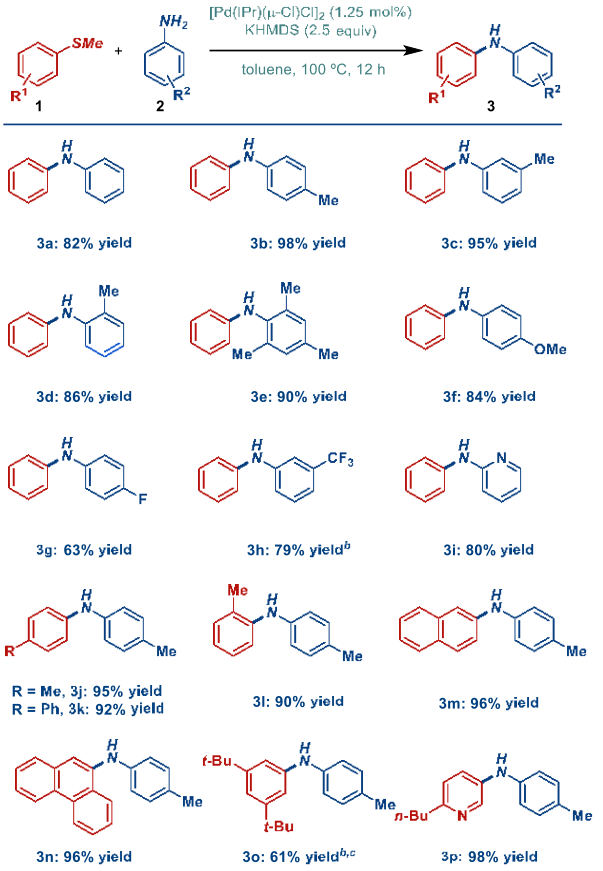
Herein, we report a combined experimental and mechanistic study on the Buchwald–Hartwig amination[14,15] and C–S/S–H metathesis[16] involving aryl sulfides by selective activation of C–S bonds (C(sp^2)–S vs. C(sp^3)–S) mediated by well-defined, air- and moisture-stable Pd(II)–NHC chloro dimers (Figure 1B).[13] We demonstrate that this class of Pd(II)–NHC pre-catalysts exhibits excellent activity in the cross-coupling of aryl sulfides by selective oxidative addition of the C–S bond.[17] Most crucially, we unravel the mechanism for activation of C–S bonds in C–N cross-coupling and C–S metathesis, where the inert C–S bond serves as a precursor to valuable amine or thioether products. We anticipate that versatile [Pd(NHC)(μ-Cl)Cl]$_2$ pre-catalysts will find broad application for C–S bond activation in organic synthesis and catalysis.

Buchwald–Hartwig Amination. From the outset, we were attracted to Buchwald–Hartwig amination of aryl sulfides owing to the fundamental role of this reaction in the synthesis of aryl amines in medicinal chemistry. Our study commenced by evaluating the reaction conditions using [Pd(IPr)(μ-Cl)Cl]$_2$ as a catalyst (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) (Table S1 and Chart S1). We established that this catalyst is highly effective for the cross-coupling using KHMDS as a base. Having established the capacity of [Pd(IPr)(μ-Cl)Cl]$_2$ as a highly effective catalyst for the C–S activation, we next evaluated the performance of different Pd(II)–NHC halo dimers and benchmarked their reactivity against other well-established Pd(II)–NHC catalysts (Table S2), where [Pd(IPr)(μ-Cl)Cl]$_2$ proved most effective. There are several key advantages of [Pd(IPr)(μ-Cl)Cl]$_2$ catalysts: (1) the catalyst is easier to synthesize than all other Pd(II)-NHC catalysts reported to date;[13d] (2) it is the fastest activating Pd(II)-NHC catalyst reported to date due to ease of dimer to monomer dissociation;[13d] (3) the catalyst is more environmentally-friendly than other Pd(II)-NHCs reported to date since there are no sacrificial heterocycles, allyl fragments or cyclometallated fragments.[12] Furthermore, in the present C–S amination, [Pd(NHC)Cl$_2$]$_2$ show superior reactivity to Pd-NHC supported by palladacycles.

Next, we sought to investigate the generality of the C–S cross-coupling mediated by the well-defined [Pd(IPr)(μ-Cl)Cl]$_2$ (Scheme 1). As shown in Scheme 1, the reaction is compatible with electronically-neutral (**3a**), electronically-donating (**3b–3f**) and electron-withdrawing (**3g–3i**) anilines. Steric substitution is well-tolerated (**3d–3e**). The cleavage of the ether group (**3f**), nucleophilic SNAr addition to aryl fluoride (**3g**) and benzylic defluorination (**3h**) were not observed under these conditions. Furthermore, the capacity to use heterocyclic anilines (**3i**) is a noteworthy feature of this protocol. The scope of the aryl sulfide component was next investigated. We found that electron-rich (**3j–3k**), sterically-hindered (**3l**) and polyaromatic sulfides, such as naphthyl (**3m**) and phenanthrenyl (**3n**) are compatible. Furthermore, *meta*-substituted (**3o**) and heterocyclic sulfides (**3p**) coupled with good efficiency. Overall, the scope study establishes [Pd(IPr)(μ-Cl)Cl]$_2$ as an effective catalyst for the synthesis of amines via this challenging C–S coupling (see SI for additional discussion). While the present study was focused on the synthesis of diaryl amines, preliminary results indicate that cross-coupling of morpholine proceeds in 40% yield under the standard conditions.[15b]

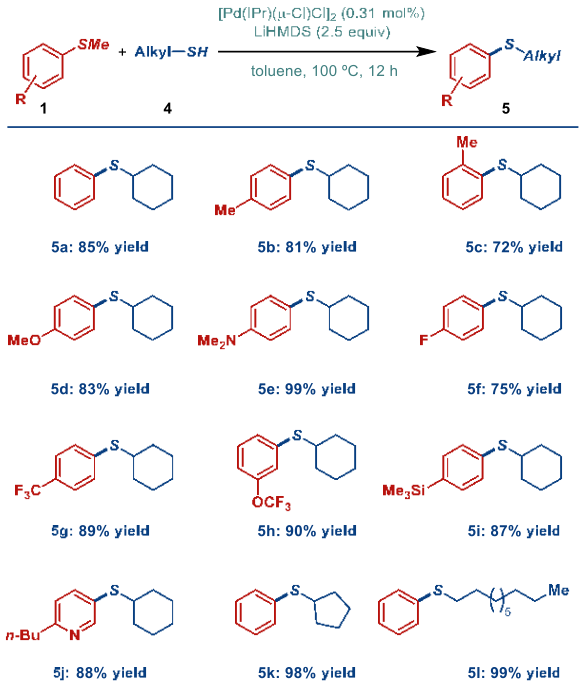
C–S/S–H Metathesis of Aryl Sulfides. Having established Pd(II)–NHC chloro dimers as versatile catalysts for C–S activation, we were intrigued by the capacity of these catalysts to mediate C–S/S–H metathesis of aryl sulfides. This attractive protocol allows for the synthesis of valuable aryl thioethers by reversible arylation. We hypothesized that the elementary C–S oxidative addition at the core of this process could lead to the identification of common features for C–S activation by [Pd(NHC)(μ-Cl)Cl]$_2$ catalysts. With this hypothesis in hand, we first examined the cross-metathesis of thioanisole with cyclohexanethiol using [Pd(IPr)(μ-Cl)Cl]$_2$ as a catalyst (Table S3). Exploratory studies revealed that the chloro-dimer [Pd(IPr)(μ-Cl)Cl]$_2$ is indeed a viable catalyst for this cross-coupling. Extensive studies of the catalyst effect established

Scheme 1. Scope of Buchwald-Hartwig Cross-Coupling of Aryl Sulfides Catalyzed by [Pd(IPr)(μ-Cl)Cl]$_2$[a]



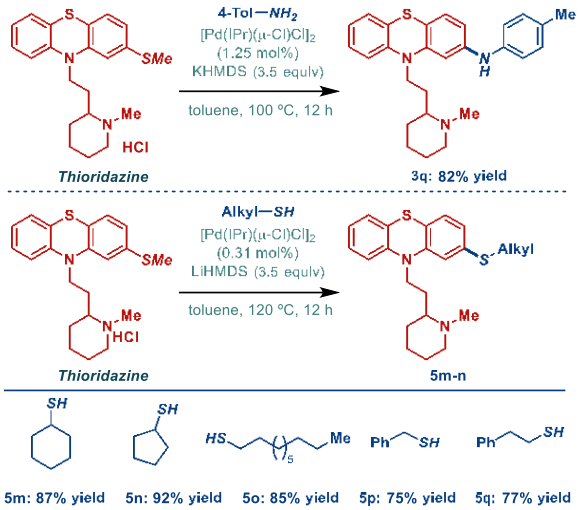
[a]Conditions: aryl sulfide (1.0 equiv), Ar-NH_2 (1.2 equiv), KHMDS (2.5 equiv), [Pd(IPr)(μ-Cl)Cl]$_2$ (1.25 mol%), toluene (1.0 M), 100 °C, 12 h. [b][Pd(IPr)(μ-Cl)Cl]$_2$ (2.5 mol%). [c]120 °C.

Scheme 2. Scope of S–C/S–H Metathesis of Aryl Sulfides Catalyzed by [Pd(IPr)(μ-Cl)Cl]$_2$[a]



[a]Conditions: aryl sulfide (1.0 equiv), alkyl-SH (2.0 equiv), LiHMDS (2.5 equiv), [Pd(IPr)(μ-Cl)Cl]$_2$ (0.31 mol%), toluene (1.0 M), 100 °C, 12 h.

Scheme 3. Derivatization of Thioridazine via Buchwald-Hartwig Cross-Coupling and C–S/S–H Metathesis of Aryl Sulfides Catalyzed by [Pd(IPr)(μ-Cl)Cl]$_2$[a]



[a]Conditions: thioridazine (1.0 equiv), Ar-NH_2 (1.2 equiv) or alkyl-SH (2.0 equiv), KHMDS (3.5 equiv) or LiHMDS (3.5 equiv), [Pd(IPr)(μ-Cl)Cl]$_2$ (0.31-1.25 mol%), toluene (1.0 M), 100-120 °C, 12 h.

that [Pd(IPr)(μ-Cl)Cl]$_2$ is the preferred catalyst (Table S4). It is worth noting that In the present C–S metathesis, [Pd(NHC)Cl$_2$]$_2$ show superior reactivity to Pd-NHC supported by palladacycles.[16a] The [Pd(NHC)Cl$_2$]$_2$ class of catalysts is superior in activation to give the same mono-ligated Pd(0)-NHC in the catalytic pathway.[13d] The key advantage of the latter is to activate the leaving group trans to the NHC ligand.

With the optimized conditions in hand, the scope of C–S/S–H metathesis catalyzed by [Pd(IPr)(μ-Cl)Cl]$_2$ was next examined (Scheme 2). This metathesis is successful with a range of electronically-differentiated thioanisoles, such as neutral (**5a**), electron-rich (**5b–5e**) and electron-withdrawing (**5f–5g**). Steric hindrance is well-tolerated (**5c**). Cleavage of the C–O (**5d**), C–N (**5e**) and C–F bonds (**5f–5g**) was not observed under these conditions. Medicinally relevant functional groups, such as trifluoromethyl ethers (**5h**), and functional handles, such as TMS (**5i**) are also compatible. Importantly, heterocyclic thioanisoles may be employed to generate medicinally relevant thioethers (**5j**) (*vide infra*). We were also pleased to find that different cyclic and aliphatic thiols, such as cyclopentylthiol (**5k**) and decanethiol (**5l**) deliver excellent levels of efficiency. The effect of different *S*-leaving groups was also optimized (Table S5). We found that various S–alkyl and S–Ph electrophiles are compatible. In our studies, we utilized C–S/S–H metathesis driven by the release of the alkyl thiol. We also investigated the effect of Pd(II)–NHCs on the reversible arylation of aryl sulfides (Table S6).

Late-Stage Functionalization. Next, we applied this catalysis manifold to the late-stage functionalization of thioridazine, an antipsychotic used for treatment of schizophrenia (Scheme 3). The common presence of the privileged C–S motif in drugs and advanced pharmaceutical intermediates renders the C–S activation platform especially useful for rapid generation of libraries of compounds for biological testing. Gratifyingly, we found that this [Pd(IPr)(μ-Cl)Cl]$_2$ mediated technology could readily generate C–N and C–S cross-coupling products in excellent yields for amination (**3q**) and thiolation (**5m–5q**) under standard reaction conditions. We also used this advanced cross-coupling to

elaborate the scope of thiols; pleasingly, the scope was found to be compatible with cyclic (**5m-5n**), aliphatic (**5o**), benzylic (**5p**) and activated thiols prone to β-hydride elimination (**5q**),[11a] attesting to the generality of the protocol in complex settings.

Density Functional Theory Studies. To gain insight into the mechanism of these intriguing C–S amination and C–S metathesis processes and to establish a unified mechanism for C–S bond activation, extensive DFT studies were conducted. Firstly, the reaction profile that leads to the catalytic active Pd(0) species was calculated and results are shown in Figure 2. For both RH agents involved, either R = NHPh(*p*Me) or SCy, the reaction is the same qualitatively. It consists of a series of dissociative/associative steps. Once the $[Pd(IPr)(\mu\text{-}Cl)Cl]_2$ dimer is cleaved, two KHDMS molecules dispose of both chlorides at the metal. Initially with the release of a KCl molecule, capturing then the proton on the R group and thus finally facilitating the release of a HHDMS molecule. Note that the thermodynamics are significantly favored when R = SCy, since the acidity of $NH_2Ph(p\text{Me})$ is significantly lower than that of HSCy, quantitatively the cost to remove a proton from HSCy is lower by 18.9 kcal/mol.

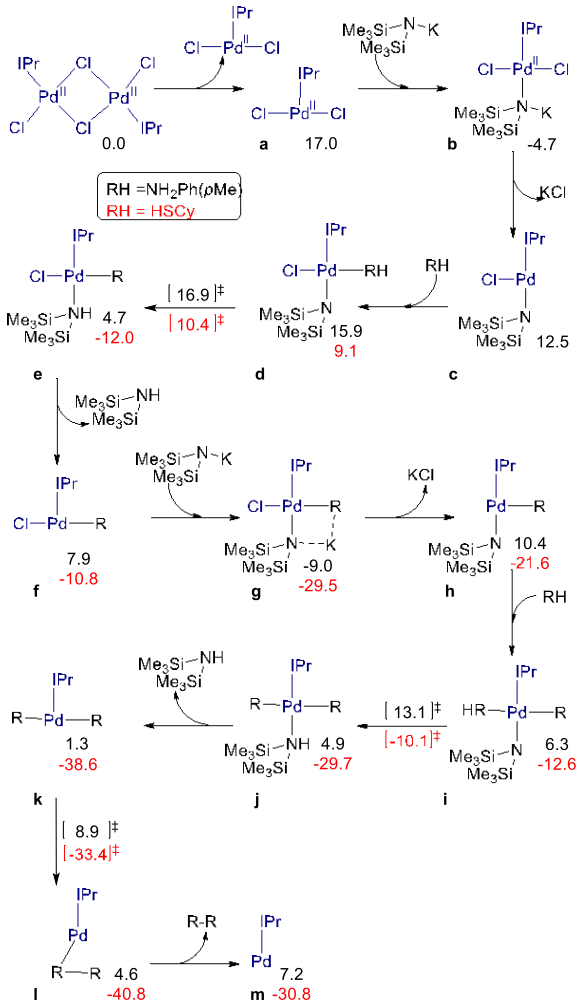


Figure 2. Reaction pathway of the initiation of the Pd-catalyzed Buchwald-Hartwig cross-coupling of aryl sulfides (in black) and C–S/S–H metathesis of aryl sulfides (in red), calculated at the M06/Def2TZVP~SDD//BP86-d3(PCM,THF)/SVP~SDD level (relative Gibbs energies at 373.15 K with respect to with respect to the dimer $[Pd(IPr)(\mu\text{-}Cl)Cl]_2$).

On the other hand, kinetically all steps are facile, and the most kinetically demanding step of the initiation is the protonation of the $N(SiMe_3)_2$ moiety by the substrate via a direct H-transfer, with an overall kinetic cost due to the transition state (TS) **i→j** of 22.1 and 19.4 kcal/mol with $NH_2Ph(p\text{Me})$ and HSCy, respectively, taking intermediate **g** as reference. Thus, the activation is significantly less kinetically demanding than with [Pd(IPr)Cl(allyl)] analogous complexes, by roughly 10 kcal/mol.[13d,18] Figure 3 displays a simple but kinetically demanding catalytic pathway. Additional discussion in presented in SI.[19-22]

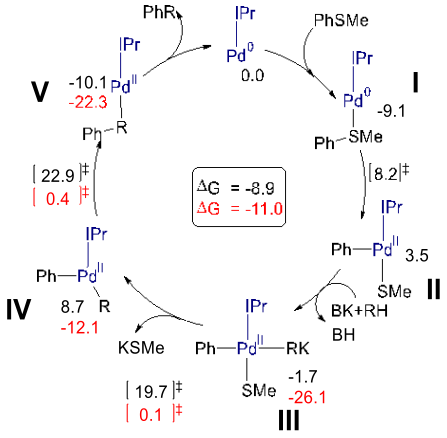


Figure 3. Catalytic pathway of the Pd-catalyzed Buchwald-Hartwig cross-coupling of aryl sulfides (in black) and C–S/S–H metathesis of aryl sulfides (in red), calculated at the M06/Def2TZVP~SDD//BP86-d3(PCM,THF)/SVP~SDD level (relative Gibbs energies at 373.15 K with respect to the catalytic active species NHC-Pd(0)). In the middle included are the thermodynamic values of the catalytic cycle.

In summary, we have reported a combined experimental and computational study on the Buchwald–Hartwig amination and C–S/S–H metathesis of aryl sulfides by selective activation of C–S bonds mediated by well-defined, air- and moisture-stable Pd(II)–NHC chloro dimer precatalysts, $[Pd(NHC)(\mu\text{-}Cl)Cl]_2$. These catalysts show excellent reactivity in the cross-coupling of aryl sulfides by a process involving oxidation addition of the aryl C–S bond. The experimental and mechanistic studies unraveled the unified mechanism for activation of C–S bonds.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information Statement

Experimental procedures, characterization data, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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