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Metathesis

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Nickel-Catalyzed Inter- and Intramolecular Aryl Thioether Metathesis by Reversible Arylation

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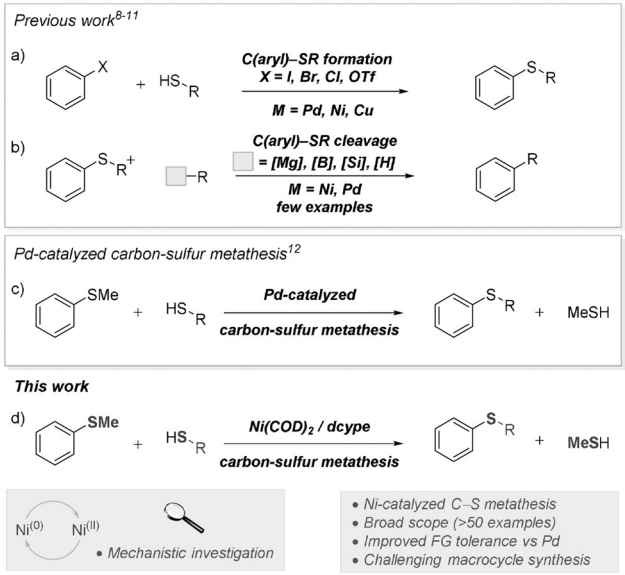
Abstract: *A nickel-catalyzed aryl thioether metathesis has been developed to access high-value thioethers. 1,2-Bis(dicyclohexylphosphino)ethane (dcype) is essential to promote this highly functional-group-tolerant reaction. Furthermore, synthetically challenging macrocycles could be obtained in good yield in an unusual example of ring-closing metathesis that does not involve alkene bonds. In-depth organometallic studies support a reversible Ni^0/Ni^{II} pathway to product formation. Overall, this work not only provides a more sustainable alternative to previous catalytic systems based on Pd, but also presents new applications and mechanistic information that are highly relevant to the further development and application of unusual single-bond metathesis reactions.*

Aryl thioethers are often found in natural products,[1] pharmaceuticals,[2–4] materials,[5] photoinitiators,[6] and fragrances.[7] Thus, the manipulation of $C(sp^2)$–S bonds has recently become an active research area in transition-metal catalysis. *The formation* of C–S bonds has greatly benefited from the advent of modern cross-coupling reactions, and a wide variety of electrophilic precursors can now be readily employed to generate complex aromatic thioethers, using a diverse range of metal catalysts such as Pd,[8a–c] Cu,[9] and Ni.[10a–c] (Scheme 1 a). In contrast, the cleavage of C–S bonds under catalytic conditions has only recently become a subject of intense research efforts in catalysis (Scheme 1 b). In these reactions, the thioether group can effectively act as an alternative to traditional cross-coupling handles such as (pseudo)halogens, thereby providing new approaches to synthesize and derivatize complex synthetic intermediates.[11a–h]

We have recently introduced a new concept for the manipulation of thioethers that involves both the formation and cleavage of carbon–sulfur bonds through a reversible single-bond metathesis process[12,13] (Scheme 1 c). However, the previously reported Pd-based catalytic system exhibited several limitations with regards to potential applications: 1) the cost of the Pd precatalyst can be prohibitive for larger-scale reactions;[14] 2) the scope with respect to the alkyl thiols was limited to unfunctionalized compounds, thus precluding many synthetic applications such as ring-closing reactions; 3) the lack of mechanistic information about the reaction limits further catalyst development.



Scheme 1. Context of the work.

Herein, we report a nickel system for the C–S bond metathesis of a broad range of functionalized coupling partners (Scheme 1 d). The improved reactivity of the Ni system was key to developing the first example of a ring-closing metathesis reaction of C–S bonds that enables rapid access to synthetically challenging macrocycles. The isolation and characterization of three catalytically competent complexes provide clear support for a Ni^0/Ni^{II} catalytic cycle.

We began our investigation using $Ni(COD)_2$ as a precatalyst and thioanisole and cyclohexanethiol as benchmark substrates. Initial evaluation of different ligands led to the recovery of starting materials (see Table S1 in the Supporting Information). After detecting the metathesis product in 8% yield after using Xantphos as a ligand, we evaluated several other bidentate phosphine ligands. The combination of a 1,2-bis(dicyclohexylphosphino)ethane (dcype) ligand and $Ni(COD)_2$ (5%) gave the best result, with the product obtained in 95% yield.[15a–c]

A wide range of thioanisole derivatives worked efficiently with the Ni catalyst (Table 1). Indeed, electron-neutral (**3aa**,

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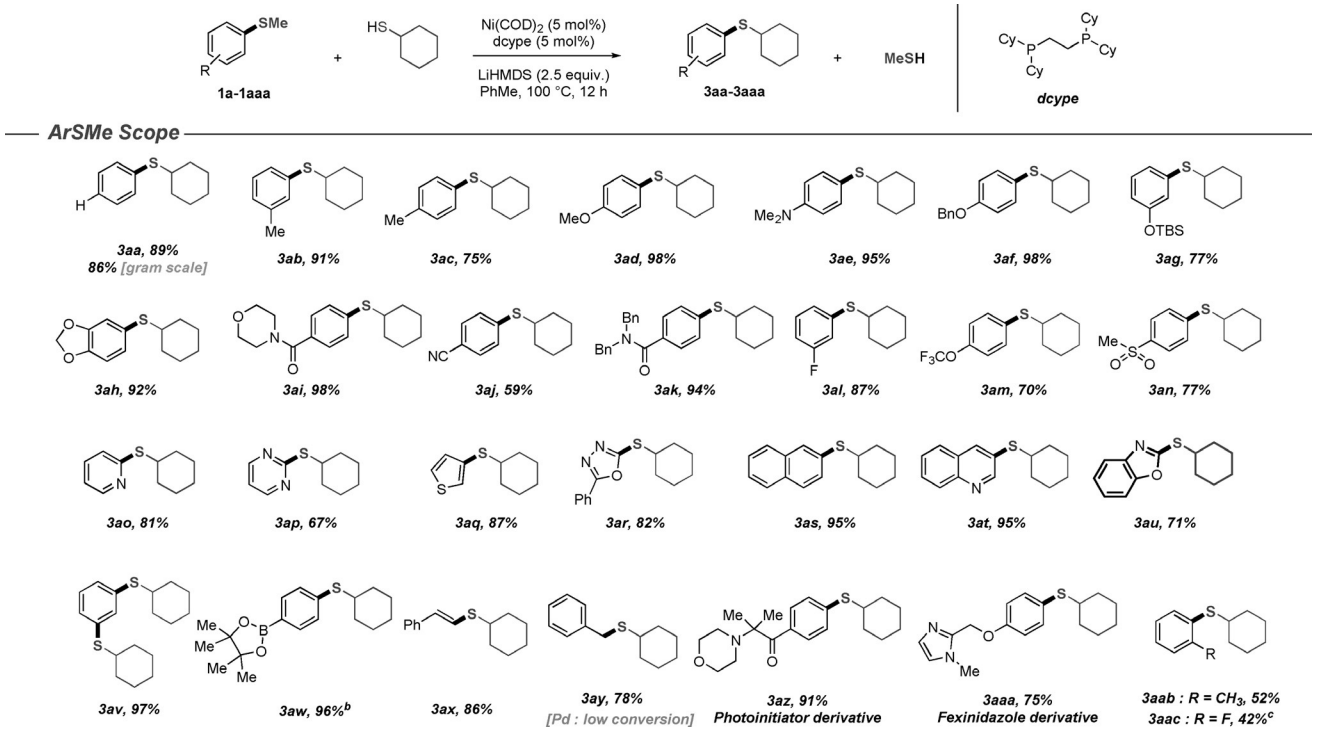
Table 1: Substrate scope with respect to thioanisoles.[a]



[a] Yield of isolated product (%). For conditions, see the Supporting Information. [b] NMR yield. [c] Reaction was performed in *o*-xylene at 140 °C.

3ab and **3ac**), electron-rich (**3ad**, **3ae**, **3af**, **3ag** and **3ah**), and electron-poor (**3ai**, **3aj**, **3ak**, **3al**, **3am** and **3an**) arenes were tolerated under our reaction conditions, providing the desired products in good to excellent yield. This method proved to be highly efficient in the presence of heterocyclic compounds (**3ao**, **3ap**, **3aq** and **3ar**). Bicyclic compounds such as naphthalene (**3as**, 95%), quinoline (**3at**, 95%) and benzoxazole (**3au**, 71%) were also found to be competent. Product (**3ax**) was obtained in 86% yield, thus demonstrating that alkenyl substrates are suitable substrates for the reaction. The reaction also worked with a thiomethylether in the benzylic position, affording (**3ay**) in 78% yield, which hints at the possibility to reversibly cleave activated C(sp^3)–S bonds under nickel catalysis. Notably, the same reaction using the previously reported palladium system resulted in poor conversion. Commercially relevant molecules bearing a thioanisole moiety were modified next. The widely used photoinitiator MMMP[6] led to product (**3az**) formation in 91% yield. A derivative of fexinidazole, a drug for treating sleeping sickness,[16] also resulted in the formation of the desired product (**3aaa**) in 75% yield, thus demonstrating the potential of this reaction for derivatizing ArSR-containing bioactive molecules. Notably, this method proved to be efficient with arenes bearing an *ortho* substituent (**3aab** & **3aac**). Remarkably, as little as 0.5 mol% of the catalyst was sufficient to reach 86% yield on a larger scale (**3aa**), a result that clearly shows that the more sustainable nickel system can be as active as palladium.

Next, we evaluated the scope of the reaction with regards to the thiol partner (Table 2), since only few functionalized thiols were tested previously. We first tried readily available alkyl thiols such as primary (**2a**–**2d**), secondary (**2e**–**2g**), and tertiary (**2h**–**2j**) thiols. In all of these cases, the metathesis product was obtained in more than 80% yield. Thiocitronellol, which bears an alkene functionality that could deactivate the nickel catalyst through chelation,[17] was a competent partner, giving the expected product (**3bk**) in 93% yield. Moreover, (*S*)-thioprolinol, which contains a basic amine, also led to the coupling product (**3bl**) in good yield (80%). We further explored the scope by using alkyl thiols bearing important functional groups such as ether (**3bn**, 90%), nitrile (**3bo**, 75%), thioether (**3bp**, 91%), amide (**3bq**, 80%), sulfone (**3br**, 43%), tetrahydropyran (**3bs**, 46%), and azetidine (**3bt**, 46%) groups. The efficiency of the Ni system encouraged us to develop the first example of a ring-closing thioether metathesis, which led to the formation of the corresponding thiochromane product (**3bu**, 93%). A thiospirocycle was also obtained in a high yield (**3bv**, 93%), thereby paving the way to a new family of spirocycles. The utility of the method was finally tested in a late-stage functionalization of a vitamin E derivative, delivering **3bw** in good yield (65%).

The application of another metathesis reaction, alkene metathesis, to macrocycle synthesis has had a tremendous impact on the synthesis of drug candidates, natural products and supramolecular assemblies.[18] We thus envisaged that synthetically challenging sulfur macrocycles[19] could be accessed by taking advantage of the potential self-correcting ability of our reversible C–S bond metathesis reaction.

Having established an efficient and scalable strategy toward the thiol precursors of these macrocycles, we then optimized our reaction conditions for the macrocyclization

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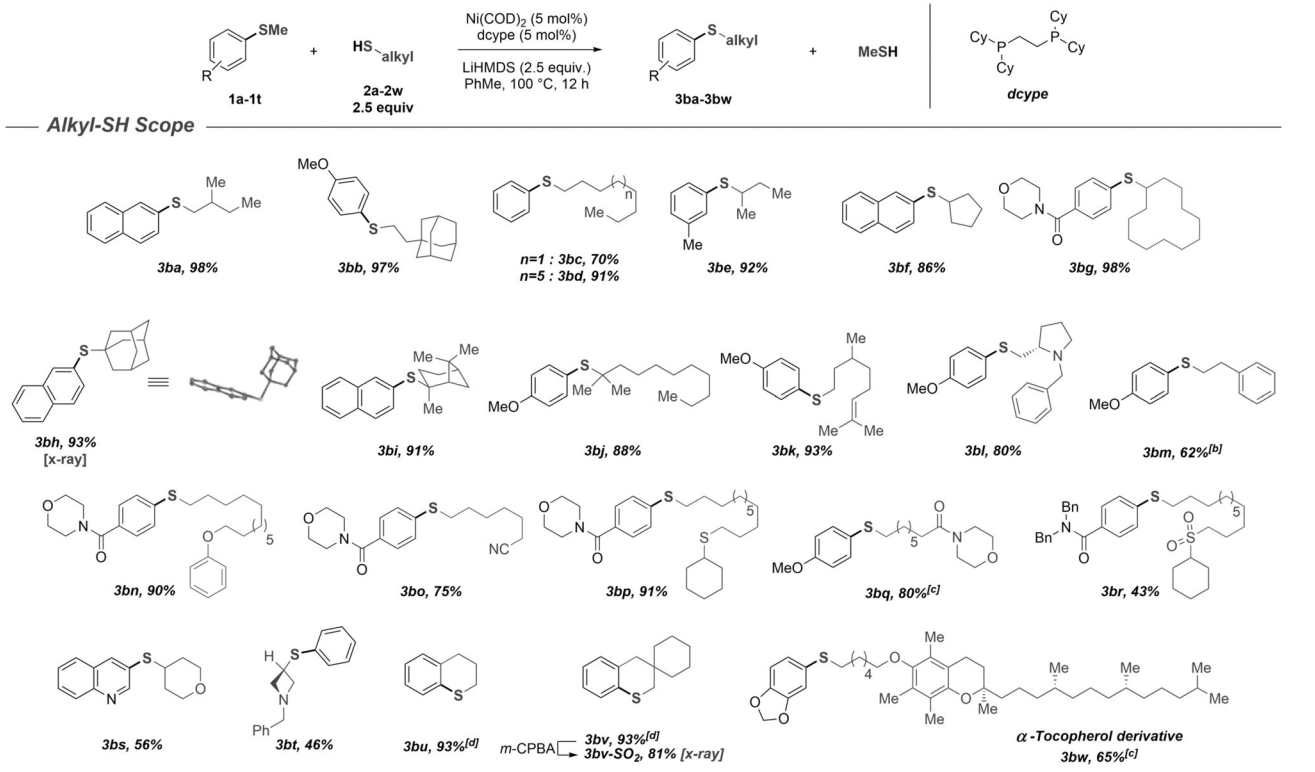
Table 2: Substrate scope with respect to alkylthiols.[a]

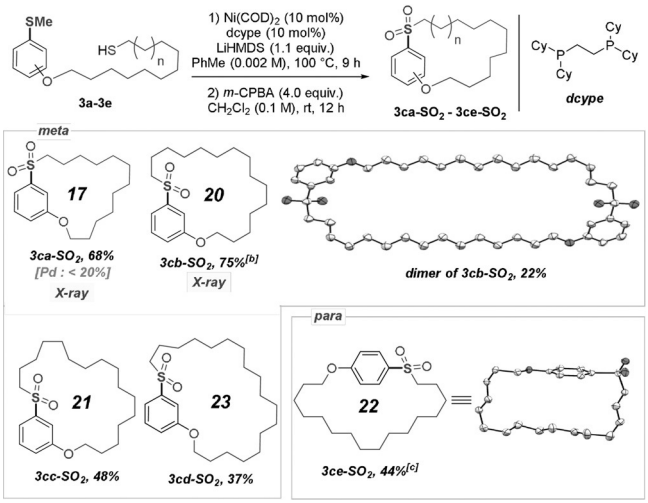


[a] Yield of isolated product (%). For conditions, see the Supporting Information. [b] Toluene (0.2 M). [c] Isolated as sulfone after oxidation with *m*-CPBA (yield over 2 steps). [d] LiHMDS (1.1 equiv).

(Table 3). The first macrocycle (**3ca**) was obtained in 68% yield using this ring-closing sulfur-bond metathesis strategy.[20a,b] Interestingly, using our previous catalytic system (Pd-SingaCycle A1), even with a higher catalyst loading of 10%, the same macrocycle was formed in less than 20% yield. This result suggests that the Pd catalyst is not active enough to catalyze the metathesis reaction under the highly diluted reaction conditions necessary for the macrocyclization. We then explored the scope with respect to starting materials bearing different chain lengths such as 15, 16, and 18 methylene units between the phenol and the thiol. All substrates readily cyclized under these conditions, affording the corresponding macrocycles (**3cb**, **3cc** and **3cd**) in 75, 48, and 37% yield, respectively. Surprisingly, the dimer of (**3cb**) was also formed under the reaction conditions in a synthetically useful 22% isolated yield, affording a rare 40-membered ring macrocycle, as confirmed by X-ray analysis. The *para* product **3ce**, which has a chain of 16 methylene units, could also be obtained in 44% yield.

While palladium-catalyzed cross-coupling processes have usually been reported to proceed via a Pd^0/Pd^{II} pathway[21a,b] the analogous nickel-catalyzed processes can proceed through different pathways because of the intrinsic higher stability of Ni^I and Ni^{III} species, although their role in catalysis has not yet been completely unraveled. While there have been examples of oxidative addition from Ni^0 to Ni^{II} species,[22a–d] with pioneering example from Itami's group on Ni-dcype catalytic system,[23] C–X (N, O, S) reductive elimination can often proceed through a Ni^{III}/Ni^I pathway, particularly in the case of nitrogen or carbene ligands.[24a,b] Indirect evidence has also been provided through computational analysis and radical trapping experiments.[11h,25a,b] In contrast, the direct observation of C–X reductive elimination from Ni^{II} is extremely rare.[26a–h] We thus became interested in

Table 3: Substrate scope of the ring-closing metathesis for macrocycle formation.[a]



[a] Yield of isolated product over 2 steps (%). 1) Substrate (0.2 mmol), LiHMDS (1.1 equiv), $Ni(COD)_2$ (10 mol%), dcype (10 mol%), toluene (0.002 M), 100 °C, 9 h. 2) *m*-CPBA (4.0 equiv), CH_2Cl_2 (0.1 M), rt, 12 h. [b] toluene (0.0025 M). [c] 24 h.

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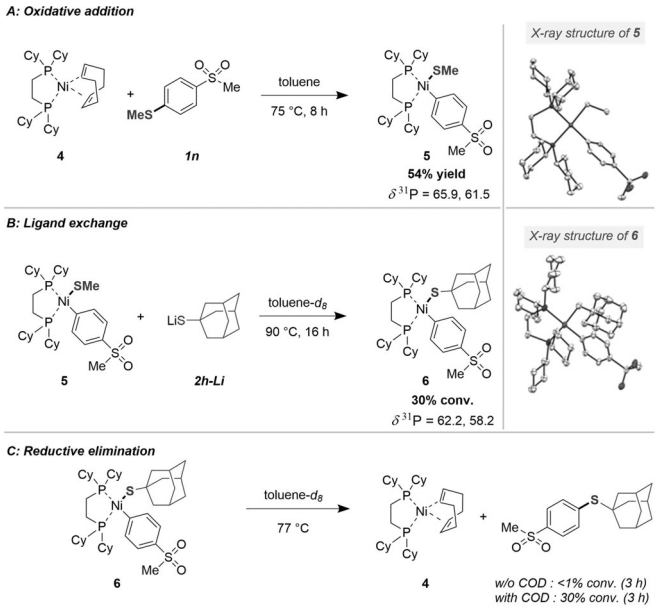
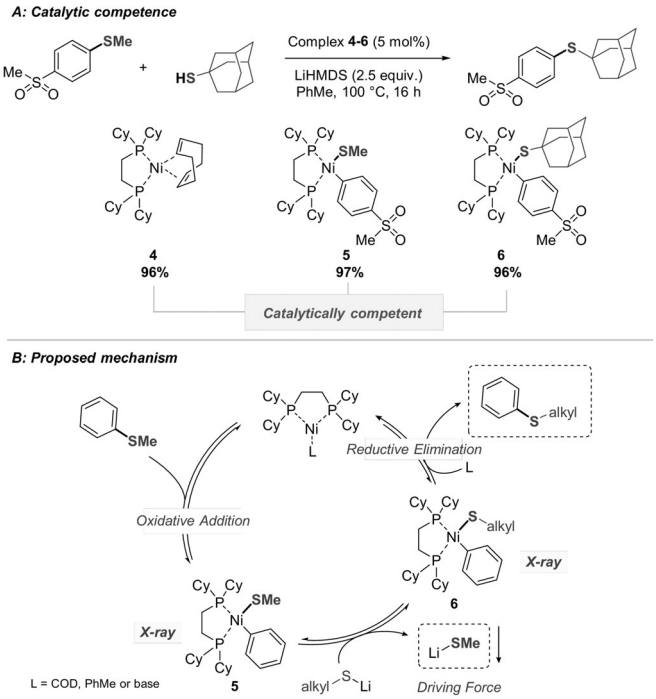
studying the reaction mechanism through stoichiometric experiments and isolation of potential organometallic intermediates. The ability of nickel complexes to span several oxidation states has been widely observed with some examples of Ni^{I} species reported as active catalysts even when starting from Ni^{0} pre-catalysts.[27a–c] To investigate this, we commenced with the synthesis of a Ni(dcype)(COD) complex[28] and tested its stoichiometric reactivity toward the aromatic thioether. We decided to use thioanisole **1n** and adamantanethiol **2h** as model substrates since their crystalline nature may ease the isolation and generation of single crystals suitable for X-ray diffraction. Treatment of nickel complex **4** with lithium adamantanethiol salt did not result in the formation of any new Ni-*ate* species (Figure S2 in the Supporting Information).

We next proceeded to evaluate the reaction of complex **4** with the thioanisole derivative **1n** (Scheme 2A). After 2 hours at 75 °C, formation of complex **5** was observed by $^{31}P\{H\}$ NMR with resonances at $\delta = 65$ and 61, leading to product isolation (54% yield) after 16 hours (Figure S3). Single-crystal X-ray analysis confirmed the identity of the oxidative addition product **5** (Scheme 2A). The putative transmetallation step was next studied through a stoichiometric experiment between complex **5** and the isolated Li adamanthylthiol salt (Scheme 2B). The reaction was very slow at room temperature, however, increasing the temperature to 90 °C resulted in the formation of a new set of doublets ($\delta = 62$), reaching up to 30% conversion overnight (Figure S5). Unfortunately, it was not possible to isolate a suitable crystal for X-ray analysis. Alternatively, we were able to gather complementary information by synthesizing complex **6** through a different pathway. Oxidative addition of adamanthyl S-phenyl to complex **4** gave complex **6** in 50% yield (Figure S4). Gratifyingly, the $^{31}P\{H\}$ NMR resonances matched the resonances of the previously observed compound, (Scheme 2B), thus confirming the viability of the transmetallation step. The identity of complex **6** was further confirmed by X-ray analysis. While reductive elimination from Ni^{III} has often been reported,[24,25] such a pathway is not viable under our catalytic conditions because of the microscopic reversibility principle. Reductive elimination from Ni^{II} complex **6** provides a more reasonable pathway to close the catalytic cycle (Scheme 2C). Interestingly, complex **6** could only undergo reductive elimination in the presence of 2 equivalents of COD (Figures S6 and S7), while the catalytic reaction can, in contrast, proceed with substoichiometric COD. This result is consistent with a reversible reductive elimination process with a small equilibrium constant favoring the oxidative addition complex **6**. Under stoichiometric conditions, the addition of COD is thus necessary to shift the equilibrium toward the product. We next confirmed the catalytic competence of complexes **4** to **6** by using 5 mol% of each complex under standard reaction conditions (Scheme 3A).



Scheme 2. Mechanistic investigation.



Scheme 3. a) Catalytic competence. b) Proposed mechanism.

Based on the aforementioned mechanistic investigation and additional unsuccessful radical-trapping experiments,[29] we propose a fully reversible catalytic cycle based on a Ni^{0}/Ni^{II} pathway (Scheme 3B). The reaction is likely to start with oxidative addition of the S–Ph bond, followed by transmetallation between Ni–SMe and alkylS–Li and final reductive elimination to release the product. Although the intermediacy of a short-lived Ni^{I} or Ni^{III} species cannot be completely ruled out at this stage, our mechanistic experiments strongly support the Ni^{0}/Ni^{II} pathway.

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Conflict of interest

A patent application for C–S metathesis has been filed (WO2018162364).

Keywords: macrocycles · reaction mechanisms · metathesis · nickel · thioethers

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[29] See the Supporting information for more details (Section 7, part c).

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