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Safe, Scalable, Inexpensive, and Mild Nickel-Catalyzed Migita-like C–S Cross-Couplings in Recyclable Water

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Abstract: A new approach to C–S couplings is reported that relies on nickel catalysis under mild conditions, enabled by micellar catalysis in recyclable water as reaction medium. The protocol tolerates a wide range of heteroaromatic halides and thiols, including alkyl and heteroaryl thiols, leading to a variety of thioethers in good isolated yields. The method is scalable, results in low residual metal in the products, and is applicable to syntheses of targets in the pharmaceutical area. The procedure also features an associated low E Factor, suggesting a far more attractive entry than is otherwise currently available, especially those based on unsustainable loadings of Pd catalysts.

Thioethers are widely distributed throughout nature, including being found in numerous physiologically active compounds. Unfortunately, Migita cross-couplings that lead to carbon-sulfur (C–S) bond formation remain challenging in several ways, including the typically high loadings of endangered Pd[1] catalysts attributed to strong coordination of thiolates to the metal, oftentimes leading to catalyst deactivation and hence, overall low efficiency.[2] Perhaps not surprisingly, therefore, development of methodologies aimed at construction of C–S bonds remains a topic of considerable interest.[3] Much of the effort, however, focuses on use of precious and expensive metals, such as palladium,[4] iridium,[5] rhodium,[6] and along with nickel[7] and ruthenium,[7] high temperatures are typically needed in waste-generating organic solvents.[8] Recently, alternative routes have emerged that call for milder conditions using photoredox catalysis,[5][9] and less costly metals such as copper,[10] cobalt,[11] or nickel.[5][7][13] Nonetheless, they oftentimes rely on the presence of additional expensive metals (e.g., Ir),[5] can involve forcing conditions, and always require organic solvents, sometimes to the strict exclusion of moisture.[7] Moreover, most rarely include direct applications to highly functionalized products, especially those characteristic of pharmaceuticals (Fig. 1). And while recent reports involving electrochemical approaches look enticing,[12] they also tend to involve high loadings of metal catalyst and are run in dipolar aprotic media, e.g., DMF, which are either being phased out or are currently prohibited, e.g., under REACH in the EU.[14] Clearly, an alternative protocol that replaces dangerously flammable and toxic organic solvents with safe, recyclable water, and that minimizes the investment of both energy and a metal catalyst that is also subject to recycling would help greatly in working towards an environmentally responsible solution to most of these challenging issues. In this report we describe such a process that relies on low levels of base metal (nickel) catalysis enabled by aqueous micellar catalysis. This new technology involves a readily available catalyst, is used under mild conditions, and is scalable; hence, it is both environmentally responsible as well as available for immediate use.

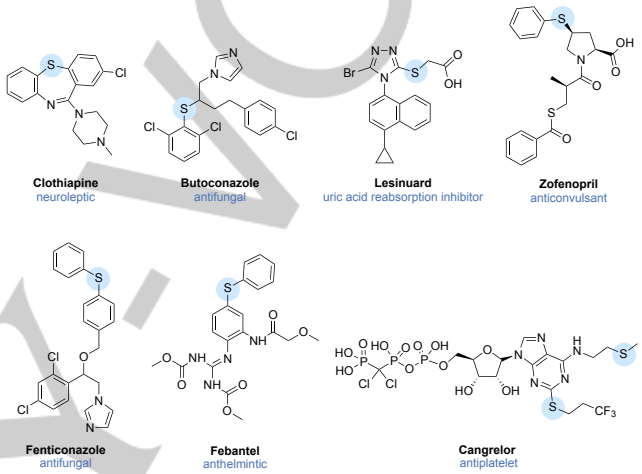

Figure 1. Selected examples of therapeutic agents bearing aromatic/heteroaromatic thioethers.

Pre-ligated nickel in the form of $Ni(Phen)_2Br_2$ (Phen = phenanthroline) was selected as pre-catalyst to test its activity in the coupling between decanethiol and 4-methoxyiodobenzene in 2 wt % TPGS-750-M aqueous solution (Table 1). Remarkably, the desired C−S cross-coupling occurred smoothly using only a 5% molar excess of thiol. Complete conversion occurred in the presence of only 2 mol % of this Ni(II) species, in the presence of zinc nanopowder (2 equiv) and anhydrous K_3PO_4 (2 equiv; entry 1). Inferior results were noted upon reducing the amount of pre-catalyst to 0.35 mol % or below (entries 2–4). Decreasing the base to 1.2 equivalents, fortunately, did not affect conversion (entry 5), but the necessity of its presence for (presumably) activation of the nucleophile was established (entry 6). Running this coupling at room temperature (22 °C) gave a significant reduction in yield over the same period of time at 45 °C (entry 7). Notably, screening the loading of Zn in the 0.1−1.0 equivalent range confirmed that only 0.25 equivalents were required (entries 8–11). By contrast, previous literature using the Ni/Zn combination involves super-stoichiometric zinc.[15] When air remained within the reaction vessel (entry 13) reaction efficiency was reduced, as thiols, not surprisingly, were oxidized under these mildly basic conditions (pH = 7–9) to disulfides.[16]

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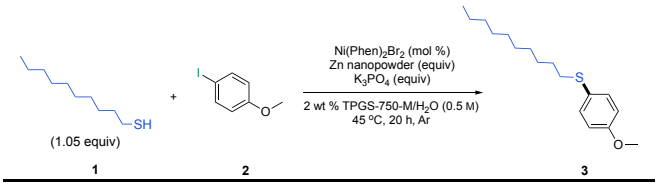
Table 1. Optimization of equivalents of catalyst and base.[a]



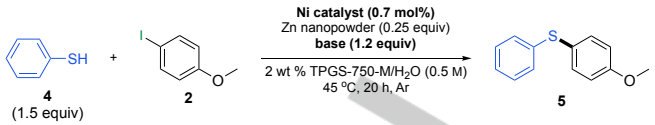
Entry	$Ni(Phen)_2Br_2$	Zn (equiv)	K_3PO_4 (equiv)	Conv. [%][b]
1	2 mol %	2	2	100
2	0.35 mol %	2	2	77
3	0.07 mol %	2	2	79
4	0.0035 mol %	2	2	53
5	2 mol %	2	1.2	100
6	2 mol %	2	0	0
7	2 mol %	2	2	6[c]
8	0.7 mol %	1	1.2	100
9	0.7 mol %	0.5	1.2	99
10	**0.7 mol %**	**0.25**	**1.2**	**94 (96)**
11	0.7 mol %	0.1	1.2	83
12	0.7 mol %	0.5	1.2	100
13	0.7 mol %	0.5	1.2	62[d]

[a] Scale of reaction: 0.25 mmol of 4-iodoanisole and 2 wt % TPGS-750-M/H_2O (0.5 mL). [b] Conversion determined by ^1H NMR. Isolated yields in parenthesis. [c] Run at rt (22 °C). [d] Run in air; disulfide formed.

In comparison with other ligands, bipyridine gave similar yields to those obtained using phenanthroline (Table 2, entries 1–2). Phosphine ligands, however, including DPPF, DPPE, and DPPB, led to significantly lower yields (entries 3–5). Locating two methyl groups on phenanthroline (i.e., neoocuproine) also impaired reaction efficiency (entry 6). Moreover, the nature of the counterion in the initial nickel salt was found to be crucial, as switching from bromide to chloride, iodide, or acetate afforded inferior results (entries 7–9). Alternative bases, including both Cs_2CO_3 and KO*t*-Bu, were found to be suitable choices upon screening (entries 10–11). Control studies revealed that both the nickel catalyst and zinc powder were essential elements (entries 12–13). The reaction failed completely when Zn was replaced by manganese,[13c] or other weak reducing agents[17] (e.g., ascorbic acid or polymethylhydrosiloxane (PMHS); entry 14).

Further evaluation of reaction conditions indicated that pre-ligation of Ni performed in limited amounts of acetonitrile gave the desired coupling product in 87-88% yield (Table 3, entries 1–2). Adding the catalyst and ligands directly, but separately, into the reaction flask gave a slightly lowered yield (81%; entry 3). Use of recrystallized catalyst had a significant impact on the loading, which could be further reduced to only 0.70 mol %, while the isolated yield jumped to 95% (entries 4–5). An X-ray crystal structure of this octahedrally configured Ni(II) pre-catalyst $Ni(Phen)_2Br_2$ is shown in Figure 2.

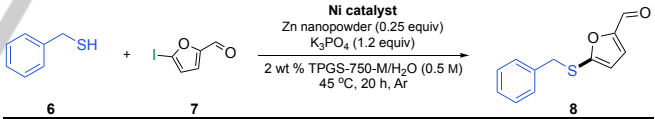
Table 2. Screening of pre-catalyst and base.[a]



Entry	Base	Ni source	Ligand	Yield [%][b]
1	K_3PO_4	$NiBr_2$	Phen	57 (66)
2	K_3PO_4	$NiBr_2$	bpy	59
3	K_3PO_4	$NiBr_2$	DPPF	19
4	K_3PO_4	$NiBr_2$	DPPB	5
5	K_3PO_4	$NiBr_2$	DPPE	5
6	K_3PO_4	$NiBr_2$	neocuproine	0
7	K_3PO_4	$Ni(OAc)_2$	Phen	18
8	K_3PO_4	$NiCl_2$	Phen	8
9	K_3PO_4	NiI_2	Phen	7
10	KO*t*-Bu	$NiBr_2$	Phen	94 (82)
11	Cs_2CO_3	$NiBr_2$	Phen	74 (71)
12	K_3PO_4	$NiBr_2$	Phen	0[c]
13	K_3PO_4	–	–	0
14	K_3PO_4	$NiBr_2$	Phen	0[d]

[a] Scale of reaction: 0.25 mmol of 4-iodoanisole and 2 wt % TPGS-750-M/H_2O (0.5 mL), Ni : ligand = 1 : 2 molar ratio. [b] Yield determined by ^1H NMR using 1,3,5-trimethylbenzene as internal standard. Isolated yields in parenthesis. [c] Run without Zn. [d] Mn, ascorbic acid, or PMHS used instead of Zn.

Table 3. Catalyst screening.[a]



Entry	[Ni]	Catalyst	Conv. [%][b]
1	1 mol %	Pre-mixed $NiBr_2$: Phen = 1 : 1[c]	87
2	1 mol %	Pre-mixed $NiBr_2$: Phen = 1 : 2[c]	88
3	1 mol %	$NiBr_2$: Phen = 1 : 2[d]	81
4	1 mol %	recrystallized $Ni(Phen)_2Br_2$[e]	94
5	**0.7 mol %**	**recrystallized $Ni(Phen)_2Br_2$[e]**	**95 (95)**

[a] Scale of reaction: 0.25 mmol of 5-iodo-2-furaldehyde and 0.5 mL of 2 wt % TPGS-750-M/H_2O. [b] Conversion determined by ^1H NMR. [c] $NiBr_2$ and phenanthroline were pre-ligated in acetonitrile and then dried. [d] $NiBr_2$ and phenanthroline were used as received. [e] $Ni(Phen)_2Br_2$ was recrystallized from EtOAc/hexane.

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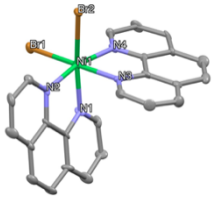


Figure 2. X-ray structure of $Ni(Phen)_2Br_2$ (CCDC 1993760). Hydrogen atoms are omitted for clarity. Refined formula: $C_{24}H_{16}Br_2N_4Ni$, formula weight M_r: 578.90. Selected bond lengths (Å): Ni1–Br1, 2.530; Ni1–Br2, 2.596; Ni1–N1, 2.105; Ni1–N2 2.063; Ni1–N3 2.092; Ni1–N 2.061.

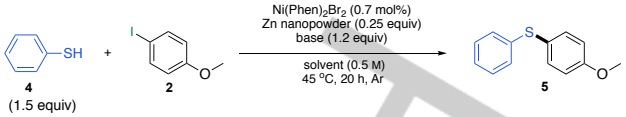
To demonstrate the crucial role played by the nanoreactors formed by the surfactant in water, comparison reactions in organic solvents (Table 4a) were studied. Under optimized conditions, nanoreactors present in aqueous solution performed competitively with commonly used, dipolar organic solvents such as DMF and acetonitrile. As shown in Table 4b, several commercially available nonionic surfactants were also evaluated. When water alone, or 2 wt % PEG 2000 in water was used, lower conversions were seen, especially in the case of more challenging reaction partners (reaction 2), mainly due to substrate polarity leading to adherence to the stirrer (Figure S1). The presence of surfactants emulsified these materials, raising the overall conversion from 56% to ca. 95%. A control experiment using this electron deficient pyridinyl bromide in reaction 2 showed, in the absence of metals, the reactivity is significantly reduced (Scheme S1). In the case of reaction 3, designer surfactant TPGS-750-M led to superior results compared to other amphiphiles, although the background reaction in its absence (i.e., "on water")[18] was somewhat competitive in this particular case (entry 1).

Under optimized conditions, the scope of these C–S couplings was extensively explored. As summarized in Table 5, most combinations of thiols and aryl iodides/bromides afforded coupled products in good-to-excellent yields.[19] Although alkyl thiols have previously been problematic in such cross-couplings due to their strong nucleophilicity that can compete with a ligand on palladium,[13d,20] both primary (leading to products **3**, **8**, **11**, **15**, **16**, **26**, **31**, **32**) and secondary alkyl (affording products **20**, **29**) thiols gave the desired thioethers to the extent of 55–96%. The reaction also took place smoothly when more complex heterocyclic thiols were involved, including use of a thiazoline giving **19**, an oxadiazole leading to **21**, a thiadiazole producing **22**, a triazole arriving at **23,** a benzothiazole yielding **24**), and a furan generating **32**.

Insofar as the aryl halide coupling partner is concerned, aryl iodides, either electron-donating (e.g., containing methoxy; see products **1** and **5**), or electron-withdrawing (e.g., bearing fluoro, as in **15** and trifluoromethyl, as in **19**), delivered the corresponding thioethers in good-to-excellent yields (70–96%). Perhaps more importantly, aryl iodides bearing reducible functional groups, such as ketone (in **16** and **21**), aldehyde (see thioethers **8**, **17**, and **29**), and ester (in **26** and **31**), were tolerated notwithstanding the presence of zinc nanopowder.[21] Aryl bromides, whether activated (e.g., leading to products **11** and **28**-**33**) or not (see product **3**) appear to undergo coupling under otherwise identical conditions.

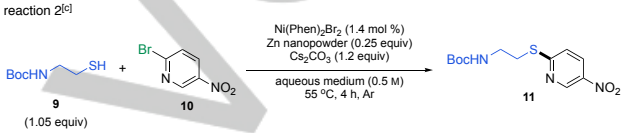
Table 4. Evaluation of the reaction medium.

(a) reaction 1[a]

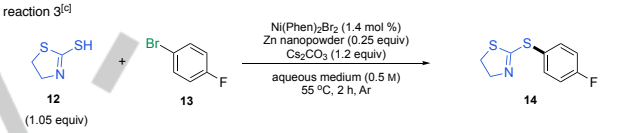


Entry	Solvent	Yield [%][b]	
		base = K_3PO_4	base = KO*t*-Bu
1	DMF	32	99
2	acetonitrile	6	59
3	**2 wt % TPGS-750-M**	**58**	**90**

(b) reaction 2[c]



(c) reaction 3[c]



Entry	Aqueous medium	Conversion [%] [d]	
		reaction 2	reaction 3
1	Pure water	56	61
2	2 wt % PEG 2000/H_2O	55	20
3	2 wt % Brij 30/H_2O	96	6
4	2 wt % Triton X 100/H_2O	95	15
5	2 wt % PTS 600/H_2O	95	19
6	2 wt % Tween 60/H_2O	94	13
7	**2 wt % TPGS-750-M/H_2O**	**95**	**66**

[a] Scale of reaction: 0.25 mmol of 4-iodoanisole (**2**) in the designated medium (0.5 mL). [b] Yield determined by ^1H NMR using 1,3,5-trimethylbenzene as internal standard. Isolated yield in parentheses. [c] 0.125 mmol 5-nitro-2-bromopyridine or 4-fluoroiodobenzene in the designated aqueous medium (0.25 mL). [d] Conversion[1] determined by proton NMR.

Nickel-based catalysts have been known to lose activity due to metal chelation by the presence of heteroatoms within either or both reaction partners, as well as by the products formed.[22] Hence, it is noteworthy that heterocyclic aryl iodides, such as those containing a furan (see **8**), thiophene (as in **18**), methylenedioxybenzenepyrazole (product **22**), or pyrazole ring (products **20** and **25**), all participated with similar efficiency. Moreover, a variety of heteroaryl bromides leading to products **28** to **33**, likewise, can be used when the loading of nickel pre-catalyst was increased from 0.7 to 1.4 mol % (or to 3 mol % in rare cases).

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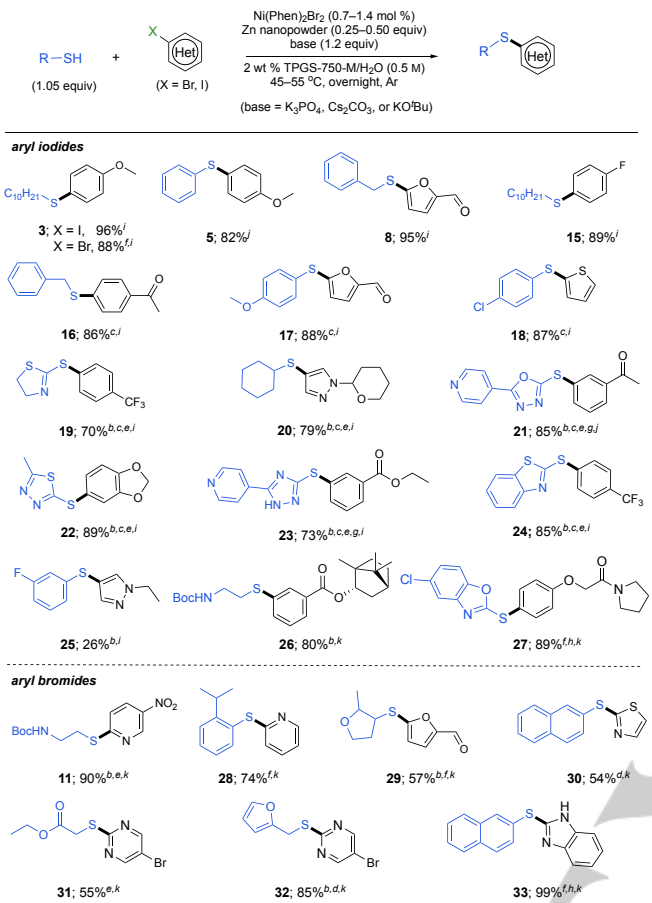
Table 5. Substrate scope.



[a] Reaction conditions unless otherwise noted: 0.25 mmol aryl bromide/iodide, 0.263 mmol thiol, 0.70 mol % $Ni(Phen)_2Br_2$, 0.25 equiv Zn, 1.2 equiv base, stirred in 2 wt % TPGS-750-M/H_2O (0.5 mL), 45 °C. Isolated yields; see SI for details. [b] Run at 55 °C. [c] 0.5 equiv Zn. [d] 1 mol % $Ni(Phen)_2Br_2$. [e] 1.4 mol % $Ni(Phen)_2Br_2$. [f] 3 mol % $Ni(Phen)_2Br_2$. [g] 10 v/v % DMSO added. [h] 10 v/v % EtOAc added. [i] K_3PO_4. [j] KO*t*-Bu. [k] Cs_2CO_3.

Particularly instructive were side-by-side comparison studies involving the preparation of problematic sulfides chosen from prior art. Examples included cases leading to pyrazoles **34** and **35**, as well as *ortho*-substituted aromatics **36** and **37**. As summarized in Figure 3, photocatalysis conditions leading to compounds **34** and **35**, calling for 2 mol % of an *iridium* catalyst together with 10 mol % nickel(II), in addition to being run in organic solvents with a costly catalyst.[5a] Conditions associated with formation of both **36** involved 10 mol % CuI,[10a] while super-stoichiometric zinc at high temperature (80 °C) were needed to synthesize compound **37**,[11a] neither of which is synthetically competitive.

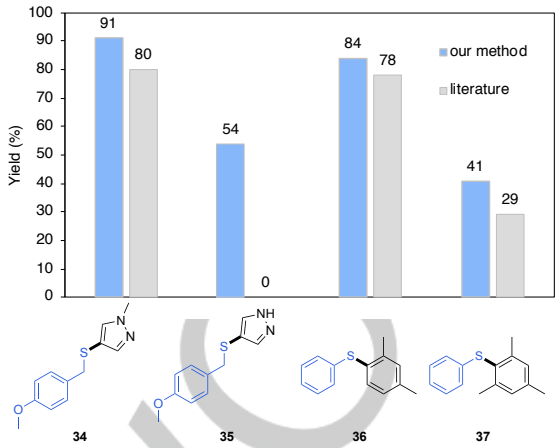


Figure 3. Selected examples of therapeutic agents bearing aromatic thioethers. Direct comparison with literature conditions. Prior art conditions: For **34** and **35**: [Ir] (2 mol %), $NiCl_2$ glyme (10 mol %), dtbbpy (15 mol %), pyridine (2 equiv), 34 W blue-LED, MeCN (0.1 M).[5a] For **36**: CuI (10 mol %), NaO*t*-Bu (1 equiv), 100-wat Hg lamp, MeCN (0.3 M), 0 °C, 5 h.[10a] For **37**: CoI_2(dppe) (1 mol %), Zn (1.5 equiv), pyridine (1 equiv), MeCN (0.25 M), 80 °C, 10 h.[11a] Current conditions: 1.4 mol % $Ni(Phen)_2Br_2$, 0.25 equiv Zn, 1.2 equiv base, stirred in 2 wt % TPGS-750-M/H_2O (0.5 mL), 55 °C, 23 h. For **36** and **37**: 0.7 mol % $Ni(Phen)_2Br_2$ was used, stirred at 45 °C, 18 h. Isolated yields.

As a meaningful application of this chemistry in water, the penultimate intermediate to Pfizer's antitumor agent axitinib (**43**) was prepared using aqueous micellar catalysis technology (Scheme 1a). Commercially available disulfide **38** was reduced with $NaBH_4$ in aqueous TPGS-750-M forming thiol **39**, generated in gram quantities. Subsequent coupling with aryl iodide **40** led to the benzopyrazole-protected sulfide, taking place in water under very mild conditions rather than the traditional use of harmful amide solvents at the reported high temperatures.[23] Without isolation, methanolic HCl was added to remove the THP group to afford **41** in 69% isolated yield over both steps.

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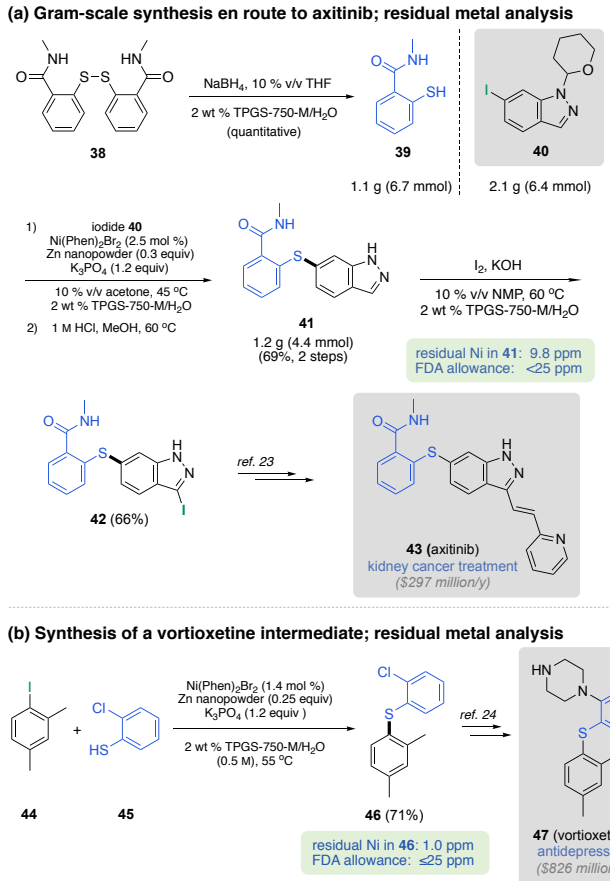
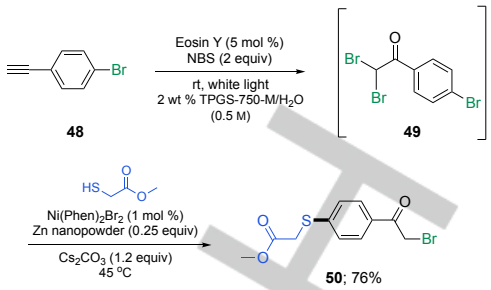


Scheme 1. Synthetic routes towards intermediates en route to axitinib and vortioxetine.

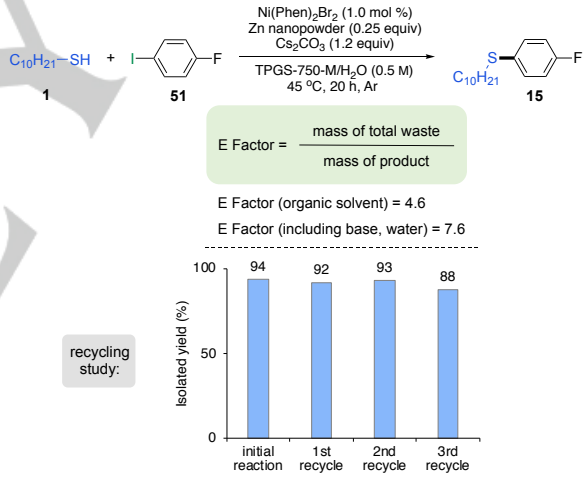
Importantly, based on ICP-MS results, residual nickel found in axitinib precursor **41** was 9.8 ppm, which is well under the limit permitted under FDA guidelines (≤25 ppm). Iodination could also be achieved under aqueous surfactant conditions, thereby reducing the amount of NMP by 90% relative to the literature route.[23] Further extension to key precursor **46** of the antidepressant vortioxetine[24] (**47**; Scheme 1b) could also be realized in 71% yield. Similar analysis of this product indicated only 1.0 ppm residual nickel.

Thioether formation can be demonstrated in tandem with photocatalysis in aqueous solution (Scheme 2). Initially, 4-bromophenylacetylene was converted to *α*,*α*-dibromoketone **49** under visible light irradiation, following the method recently developed by Handa and co-workers.[25] Subsequent nickel catalyzed thioetherification could then be effected concurrent with monodebromination facilitated by base present in the aqueous solution.[26] Noteworthy is the observation that the *α*-bromoketone product **50** remained intact under these aqueous micellar conditions.



Scheme 2. 1-Pot, 2-reaction sequence.

The aqueous reaction mixture, used throughout at substrate global concentration of 0.50 M containing 2 wt % TPGS-750-M, could be re-used in three additional reactions (Scheme 3) thereby further minimizing generation of waste water.[27] By virtue of the sub-stoichiometric amount of zinc required, reaction mixtures stirred easily, and "in-flask" extraction with minimal and recoverable MTBE allowed for isolation of the desired product. The E Factor[28] based on the organic solvent employed was only 4.6, suggesting, overall, a sustainable process is in hand for thioether bond formation.



Scheme 3. Determination of E Factors, and recycling study.

In summary, a mild and recyclable Ni-catalyzed C–S cross-coupling reaction has been developed that takes place in recyclable water under environmentally responsible micellar aqueous conditions. The process effectively promotes thio-etherification at sp^2 carbon centers with both aryl and alkyl thiols that is not only general, but is also tolerant of a variety of functionality in either or both reaction partners. Opportunities to use the aqueous medium for tandem, 1-pot applications are also demonstrated. Overall, this new technology offers an inexpensive, safe, scalable, and reliable route to aryl/heteroaryl sulfides that may find, in particular, applications to active pharmaceutical ingredients (APIs).

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Keywords: aqueous micellar catalysis • axitinib • designer surfactant • Migita cross-coupling • nickel-catalysis

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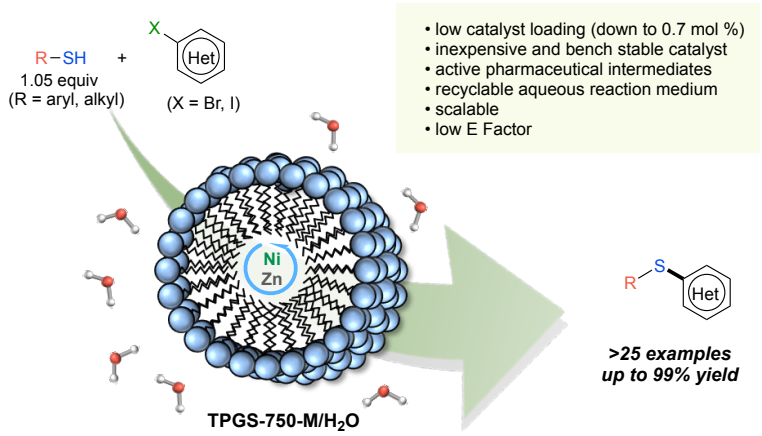

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