Ru(II)-Catalysed [1,4]-Sigmatropic Rearrangement and Intramolecular S_NAr Reaction of Aryl and Heteroarylthioacetates using Quinoid Carbene

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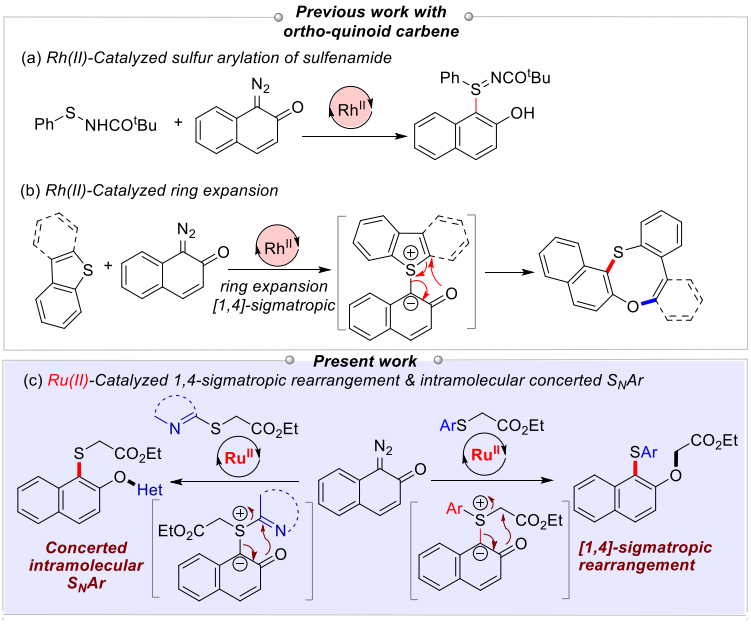
Abstract: A Ru(II)-catalyzed straightforward and efficient strategy has been developed to construct *O*-alkylated arylnaphthyl thioether derivatives using α-thioesters and diazonaphthoquinone *via* an unprecedented [1,4]-*oxa* sigmatropic rearrangement. A detailed mechanistic study reveals that the reaction is going through a concerted manner. In a complementary method, heteroarylacetate offers *O*-heteroaryl alkylnaphthyl thioether derivatives *via* a novel concerted intramolecular S_NAr-type reaction. Both these methods proceed through the formation of quinoid carbene and sulfur ylide respectively.

Diazo compounds are often considered essential precursors for carbene generation under transition metal-catalyzed synthetic transformations.[1] Among various diazo compounds, diazoquinones or quinone diazides are unique due to their structure having a planar six-membered ring with carbonyl, olefin and diazo functionalities in conjugation and offering phenol/naphthol derivatives as end products.[2] Strategically, diazoquinones and diazonaphthoquinones are applied under transition metal catalysis for C-H insertion [3] NH insertion,[4] OH insertion[5], and cyclopropanation.[6] Due to the abundance of sulfur atoms in bioactive molecules and organic materials,[7] inserting sulfur centre to quinoid carbene *via* sulfur ylide formation would be appealing. In general, sulfur ylides derived from allyl sulfides alkyl sulfides, or α-thioesters are exploited for classical [2,3] and [1,2] sigmatropic rearrangements namely Doyle-Krimse, Stevens or thia Sommlet-Hauser rearrangements with acyclic diazo compounds.[8-10] Though, there are reasonable advancements in the area of [2,3] and [1,2] sigmatropic rearrangements with acyclic diazo, development in [1,4] sigmatropic rearrangement is limited.[11] More importantly, there are only a few examples where quinoid carbene was used to afford the corresponding sulfur ylide.[12-14] In a seminal work, Ellman's group reported Rh(II)-catalyzed S-naphtholation of sulfonamides using diazonaphthoquinone (Scheme 1a).[12] Very recently, Wang's group disclosed a Rh(II)-catalyzed ring expansion of thiochromenes and aromatic thiophenes to deliver polyaromatic oxathionines and oxathiocines using *ortho*-diazonaphthoquinones derivatives via under-explored [1,4] sigmatropic rearrangement of sulfur ylide (Scheme 1b).[13] Further, Zhou's group reported a Rh(II)-catalyzed Doyle−Kirmse rearrangement/Cope rearrangement cascade reaction of

allylic sulfides under para-diazoquinone .[14] Notably, in all these cases the quinoid carbenes were generated under expensive Rh(II) catalysts. In this regard, we found that cheaper Ru-salts are less explored for such purposes. [15] Though, in a pioneering work, Che's group used ruthenium-based quinoid carbene to transfer to nitrosoarene derivatives[15b], its applications in synthetic transformations are limited. [16]

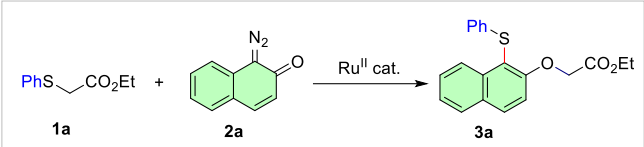


Scheme 1. Reactions of *ortho*-diazonaphthoquinone with sulfur-containing molecules a) Rh(II)-catalyzed thioarylation of sulfenamide b) Rh(II)-catalyzed ring expansion. c) Ru(II)-catalyzed [1,4]-sigmatropic rearrangement and intramolecular concerted S_NAr reaction of arylthioacetate and heteroarylthioacetate

To the best of our knowledge, there is no previous report on sigmatropic rearrangements using less expensive Ru-quinoid carbene chemistry. Among different substitution reactions on aromatic scaffolds, S_NAr reactions become important due to their regular applications in pharmaceuticals synthesis.[17] Further, this class of reactions also gained significant attention recently due to its mechanistic importance where they proceed via a concerted nucleophilic aromatic substitution pathway (cS_NAr) rather than a classically known two-step mechanism through the formation of discrete Meisenheimer complex.[18][19] Intrigued by the above works and with our previous expertise in quinoid carbene insertion[16a][20], we endeavoured that in the presence of transition metal catalysts, diazoquinone will form quinoid carbene. Next, the sulfur centre of arylthioacetates will react with quinoid carbene to provide the sulfur ylide which can further proceed to afford an *oxa*-[1,4] sigmatropic rearrangement. In addition, we also envisioned that if we replace the aryl group with a weakly stabilizing nitrogen-containing heteroaryls, the reaction might proceed through intramolecular concerted nucleophilic

aromatic substitution (cS_NAr). Herein, we report a Ru(II)-catalyzed straightforward *oxa*-[1,4] sigmatropic rearrangement of arylthioacetates and intramolecular concerted S_NAr reaction for heteroaryl thioacetates with diazonaphthoquinone to accomplish complementary S, O-protected naphthyl derivatives.

Table 1. Optimization.[a]

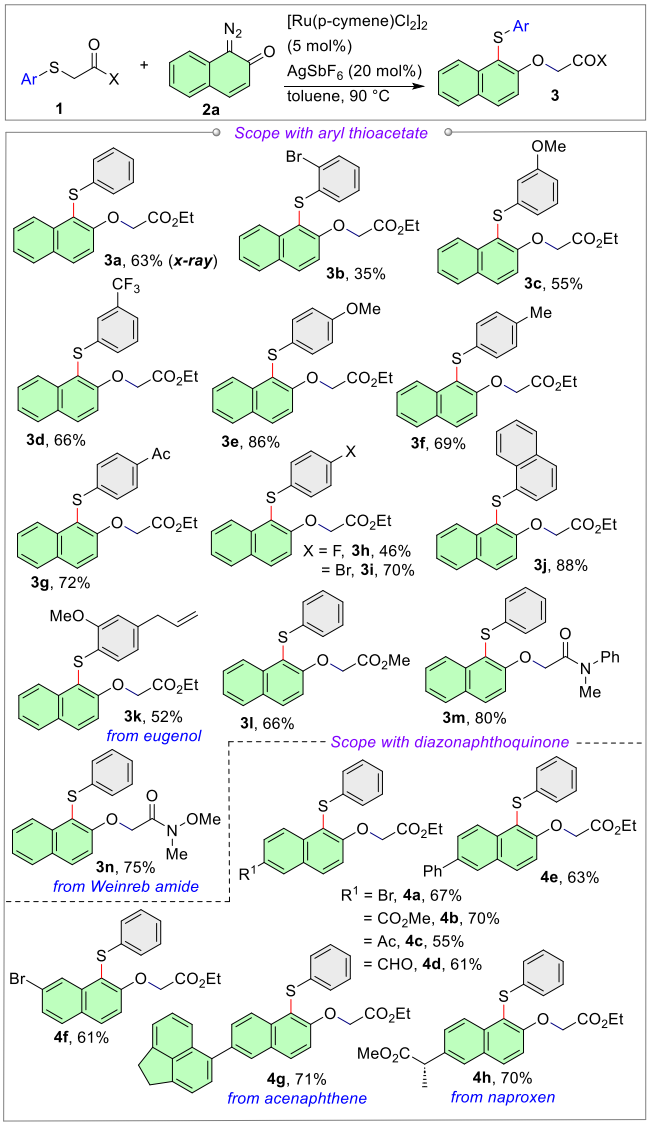


entries[b]	solvent	additive	temp (°C)	yield (**3a**) (%)[b]
1	DCE	NaOAc	80	15
2	DCE	$AgSbF_6$	80	58
3	PhMe	$AgSbF_6$	80	62
4	dioxane	$AgSbF_6$	80	48
5	CH_3CN	$AgSbF_6$	80	40
6	$CHCl_3$	$AgSbF_6$	80	51
7	PhCl	$AgSbF_6$	80	41
8	$PhCF_3$	$AgSbF_6$	80	30
9	**PhMe**	**$AgSbF_6$**	**90**	**68**
10	PhMe	$AgSbF_6$	100	55
11	PhMe	$AgBF_4$	90	42
12	PhMe	$AgNTf_2$	90	46
13	PhMe	AgOTf	90	40
14	PhMe	$AgNO_3$	90	33
15	PhMe	AgOAc	90	28
16	PhMe	Ag_2CO_3	90	26
17	PhMe	-	90	25

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), additive (20 mol%), solvent (0.1 M). [b] Isolated yields. DCE = 1,2 dichloroethane.

Based on our hypothesis, our study was initiated by model reaction with ethyl 2-(phenylthio)acetate (**1a**) and diazonaphthoquinone (**2a**) under 5 mol% $[RuCl_2(p\text{-cymene})]_2$. To optimise the reaction conditions a large number of screening was carried out (see supporting information for the detailed optimization). Partial screening results are summarized in Table 1. Initially, the reaction was done under 1,2 dichloroethane (DCE) solvent with NaOAc as additive to offer 15% yield of desired product **3a** at 80 °C (Table 1, entry 1). Gratifyingly, the change of additive with silver salt $AgSbF_6$ improved the isolated yield to 58% (Table 1, entry 2). Further screening of solvents, marginally improved the isolated yield of **3a** in 62% under toluene

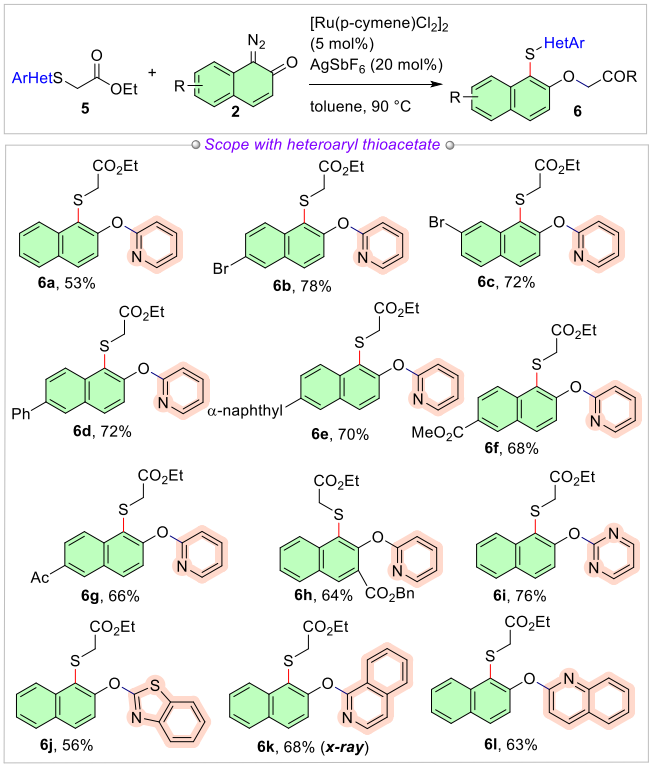
solvent (Table 1, entries 3-8). Other solvents did not perform better. When the temperature was slightly risen to 90 °C, the yield was also slightly improved up to 68% (Table 1, entry 9). However, a further increase in temperature lowered the isolated yield of **3a** presumably due to unwanted decomposition of diazoquinone (Table 1, entry 10). Next, we tested various silver salts as halide scavengers. However, none of them improved the isolated yield of the **3a** in toluene under Ru(II)-catalysed conditions (Table 1, entries 11-16). Without any additive, the reaction offered only a poor yield of the desired product **3a** (Table 1, entry 17).



Scheme 2. Scope with aryl thioacetate: Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), PhMe (0.1 M), 90 °C.

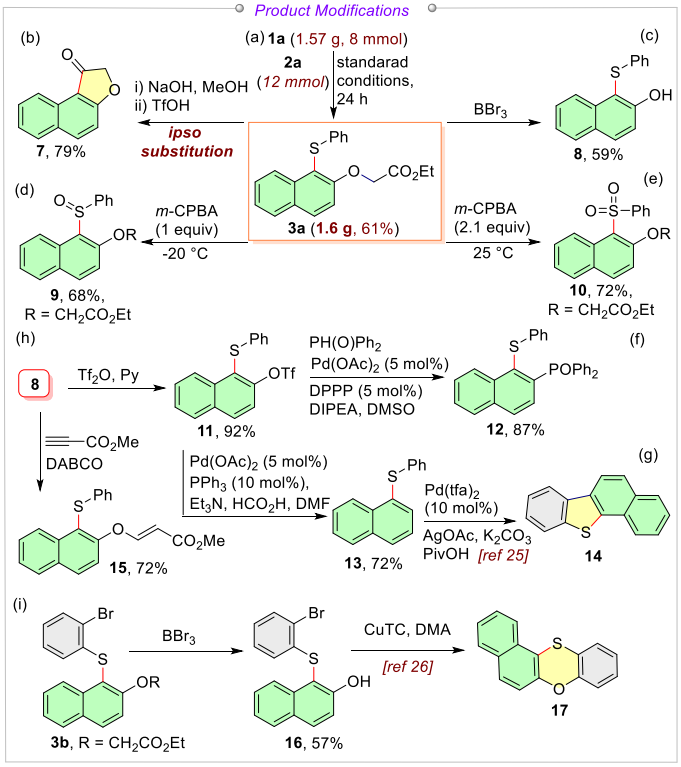
Having the best reaction conditions, we set out to find the generality of this transformation (Scheme 2). Initially, different aryl thioacetates were screened. The halide substitution at the *ortho* position of the aryl ring offered a poor yield of the desired product (Scheme 2, **3b**). Possibly, the steric bulk at the *ortho*-position restricts the formation of corresponding sulfur

ylide. Next, the electron-rich OMe or electron-withdrawing CF_3 at the *meta* position of the phenyl ring did not give significant differences in the product's yield (Scheme 2, **3c**-**3d**). Next, variations in the electronic and steric properties at the *para* position of the phenyl ring were investigated to afford the corresponding *O*-alkylated naphthol derivatives in moderate to very good yields (Scheme 2, **3e**-**3i**). Remarkably, the bulky naphthyl group also reacted smoothly to offer the binaphthyl thioether derivative (Scheme 2, **3j**). When the bioactive eugenol tethered thioacetate was explored under optimized conditions, surprisingly it provided the desired product keeping the double bond intact (Scheme 2, **3k**). This indicates that the nucleophilic sulfur centre attacks faster to the quinoid carbene centre before the reaction with the olefinic double bond. In addition, other α-aryl thioester and tertiary amides also afforded the desired products in good yields (Scheme 2, **3l**-**3n**). To demonstrate the product diversity, a broad range of diazonaphthoquinone was examined. Halide-like Br group at the different positions of the naphthyl ring accommodated good yields of the products (Scheme 2, **4a**, **4f**). Further, electron-deficient functional groups like ester and carbonyl-attached diazonaphthoquinones offered the desired products in moderate to good yields (Scheme 2, **4b**-**4d**). Furthermore, more conjugated aryl containing diazonaphthoquinone also provided the desired product (Scheme 2, **4e**).



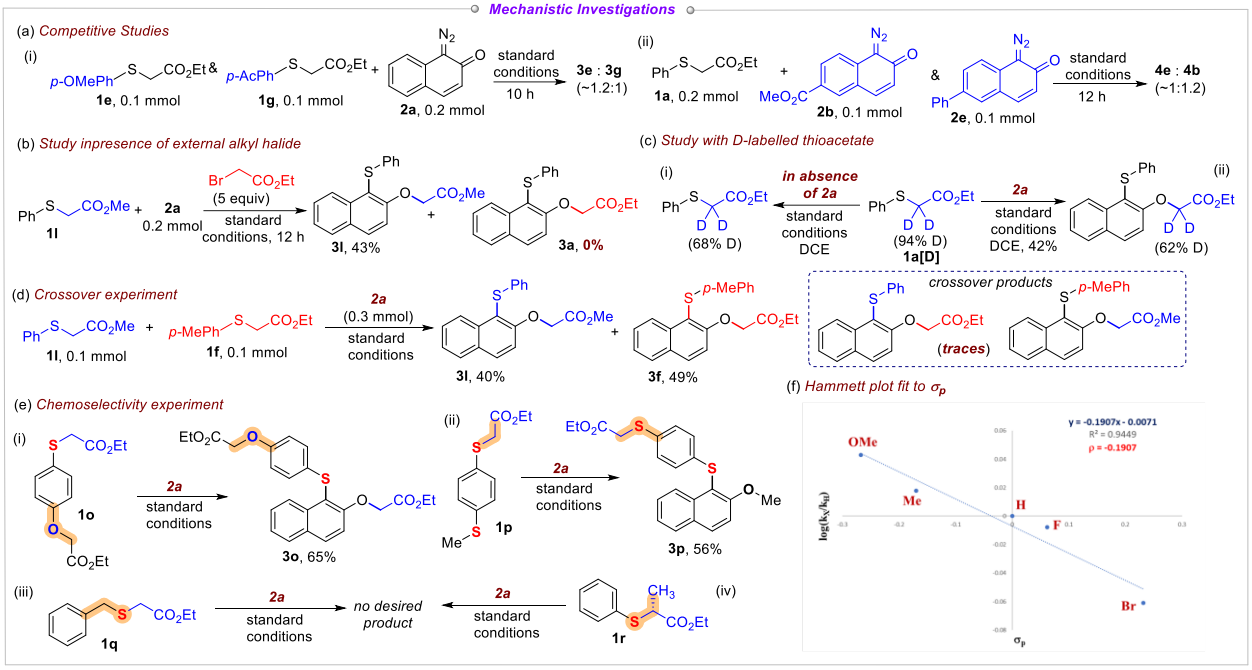
Scheme 3. Scope with heteroaryl thioacetate: Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), PhMe (0.1 M), 90 °C.

From the view of product complexity, bioactive acenaphthene and naproxen attached diazonaphthoquinone also furnished the desired products in good yields (Scheme 2, **4g**-**4h**). X-ray crystallographic structure of **3a** unequivocally confirmed the event of 1,4-sigmatropic rearrangement.[21] Nucleophilic aromatic substitution (S_NAr) is a fundamental and common reaction used in pharmaceutical and chemical research. [22] Generally, these reactions proceed *via* step-wise addition elimination reaction with the formation of a discrete Meisenheimer complex as an intermediate. Notably, in an S_NAr mechanism the Meisenheimer complex as an intermediate need to be more thermodynamically stable than the transition state (TS) for the concerted pathway. Incidentally, the S_NAr reactions extended for the synthesis of pharmaceuticals [23] including less stabilized anion or facile leaving group, the intermediates are not detectable. Recently, comprehensive studies were carried out on various substrates to challenge the classical step-wise mechanism for S_NAr reactions.[19] It has been proposed that the weakly stabilizing group for the Meisenheimer complex and the good leaving group facilitate a concerted pathway over a step-wise mechanism. We hypothesize that in the place of phenyl thioacetate (**1a**) if we use pyridylthioacetate (**5a**) it might trigger the migration of the heteroaryl ring to the oxygen centre via the S_NAr pathway. Gratifyingly, when the 2-pyridyl thioacetate (**5a**) was used as starting material under our Ru(II)-catalysed developed conditions, the *O*-pyridyl derivative S_NAr product obtained in 53% (Scheme 3, **6a**).



Scheme 4. Post Synthetic Modifications

Next, we extend the scope for 2-pyridyl thioacetates. Bromide containing diazonaphthoquines worked under optimized conditions without any issue to keep the option open for further coupling reactions (Scheme 3, **6b**-**6c**). Diazonaphthquinone with more conjugation with Ph and α-naphthyl ring offered very good yields of the desired products (Scheme 3, **6d**-**6e**). Next, electron-withdrawing ester and acetyl groups containing diazonaphthoquinone afforded the



corresponding products in good yields (Scheme 3, **6f**-**6h**). To check the generality of this S_NAr transformation, we have screened other pyridine-related heterocycles. By altering pyridine thioacetate with pyrimidine, benzothiazole, isoquinoline and quinoline thioacetate derivatives, the corresponding products were obtained in good yields (Scheme 3, **6i**-**6l**). The ^1H NMR data reveals that the signal of the CH_2 group in **6a** is in a more shielded region than the corresponding signal in **3a**.

Scheme 5: Mechanistic Investigations

Finally, the single crystal x-ray structure of **6k** confirmed the interesting intramolecular S_NAr transformation under our optimized conditions.[21] As shown in Scheme 4a, this developed protocol can be scaled up in gram-scale to give **3a** in 61% yield. Further, to exhibit the applications of the developed protocol, initially, compound **3a** was hydrolyzed and subsequent TfOH-mediated *ipso* substitution afforded corresponding naphthofuranone derivative **7** (Scheme 4b). Next, dealkylated product **8** was obtained from **3a** under BBr_3-mediated conditions (Scheme 4c). Further, **3a** was converted to corresponding sulfoxide **9** and sulfone **10** via the addition of *m*CPBA (Scheme 4d & 4e). Furthermore, naphthol **8** was converted into its triflate derivative **11** which was subsequently transformed into its corresponding phosphine

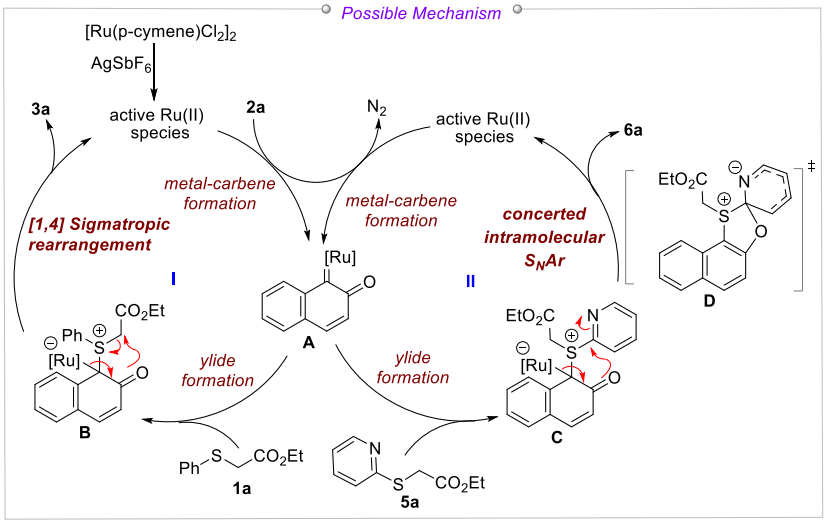
oxide **12** (Scheme 4f). Moreover, the triflate **11** was deoxygenated under Pd(II)-catalyzed conditions to afford biaryl thioether **13**.[24] Compound **13** can be converted to the benzonaphtho thiophene derivative **14** under Pd(II)-catalyzed conditions[25] (Scheme 4g). Meanwhile, compound **8** was converted to the corresponding alkoxy acrylate derivative **15** in the presence of methyl acrylate (Scheme 4h). Next, another important scope **3b** was dealkylated to its corresponding naphthol derivative **16** which can be transformed into benzo phenoxathiine scaffold *via* a CuTC catalysed known literature method[26].

After having the scope and developed product's utility, we wanted to explore the detailed mechanistic investigation for the developed protocol. A competition reaction between electronically variable thioacetates (**1e** & **1g**) revealed that there was no significant reaction rate difference between these two coupling partners [Scheme 5a(i)]. A similar trend in result was found in a competition experiment between electronically variable diazonaphthoquinones (**2b** and **2e**) [Scheme 5a(ii)]. When the reaction was carried out with methyl 2-(phenylthio)acetatein (**1l**) in the presence of **2a** and excess external electrophile ethyl-bromoacetate, there was no isolable formation of O-ethyl alkylacetate product (**3a**) (Scheme 5b). This result indicated that presumably the reaction was not going via a step-wise mechanism but followed a concerted pathway.

Further, in a control experiment, it was also realized that under the optimized conditions in the absence of diazonaphthoquinone **2a,** there was some loss (~68%) in D incorporation in compound **1a[D]** [Scheme 5c(i)]. Notably, when **1a[D]** underwent the reaction with **2a** under optimized conditions there was no additional D loss in the product (62% D) [Scheme 5c(ii)]. This outcome again suggested that the reaction was going via a concerted pathway. To confirm further the concerted pathway of the following reaction, we exposed aryl thioacetates **1l** and **1f** with **2a** under standard reaction conditions. Incidentally, there were no cross-over product formations (Scheme 5d). This result further ruled out the possibility of a step-wise mechanism. In further mechanistic investigations, the chemoselectivity of the developed protocol was shown. Substrate **1o** with arylthio acetate and oxyacetate chemoselectively formed quinoid carbene with the sulfur center to afford the product **3o** [Scheme 5e(i)]. In general, this chemoselectivity appeared due to the higher nucleophilic nature of the sulfur centre over the oxygen centre. Furthermore, a substrate with aryl thioacetae and methylthioether **1p** reacted selectively with the sulfur centre of methylthioether part to afford product **3p** [Scheme 5e(ii)]. Possibly the high electron density at the methylthioether sulfur center facilitates to generate of the corresponding sulfur ylide over the thioacetate sulfur center. When ethyl 2-(benzylthio)acetate **1q** was explored under the optimized conditions, it did not provide any desired product possibly due to the lack of thioaryl moiety in the substrate [Scheme 5e(iii)]. Notably, increased steric bulk at the α-position did not furnish the desired

product [Scheme 5e(iv)]. Next, the best linear correlation in the Hammett plot was obtained for σ_p with goodness of fit (r^2) 0.94. The negative ρ value (ρ = -0.19) obtained in the Hammett correlation implies that electron density leaves the π-system in the rate-determining step. Moreover, the low ρ value also suggests that the developed reaction has marginal substituent effects (Scheme 5f).

Based on previous literature[9][11][19] and mechanistic studies, a probable mechanism was proposed (Scheme 6). First, the $[RuCl_2(p\text{-cymene})]_2$ catalyst formed the active Ru(II)-catalyst in the presence of halide scavenger Ag salt. Next, it formed the Ru-based quinoid carbene species **A** with the **2a**. Further, for catalytic cycle I, ylide **B** was generated from **A** during the reaction with aryl thioacetate **1a**. In a concerted manner, ylide **B** underwent concerted 1,4-*oxa* sigmatropic rearrangement to afford compound **3a** with the regeneration of an active Ru(II) catalyst. When heteroarylacetate **5a** was used with quinoid carbene **A**, the transformation proceeds via catalytic cycle II through the formation of ylide **C**. In contrast to arylthioacetate **1a**, when **5a** was used as the starting thio compound, ylide **C** formed compound **6a** via an intramolecular S_NAr manner through the formation of transition state **D.** Notably, this was only weakly stabilized by nitrogen-containing heterocycle and an excellent leaving group. These factors might be expected to favour a concerted intramolecular S_NAr-type transformation to afford **6a**.



Scheme 6: Possible Mechanism

In summary, we have developed a Ru(II)-catalyzed straightforward and efficient strategy using α-thioesters and diazonaphthoquinone to construct *O*-alkylated arylnaphthyl thioether derivatives via an unprecedented [1,4]-*oxa* sigmatropic rearrangement.[Detail mechanistic investigations reveal that the developed method follows a concerted mechanistic pathway. Further, in a complimentary method under similar reaction conditions, heteroarylacetate

offered *O*-heteroaryl alkylnaphthyl thioether derivatives *via* a novel concerted intramolecular S_NAr type reaction. Both these reactions proceed *via* the formation of quinoid carbene and sulfur ylide respectively. Post-modifications of the synthesized compounds lead to various extended conjugated systems.

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Conflict of Interest

The authors declare no conflict of interest

Data Availability Statement

The supporting data of this study are available in the supplementary material of this article.

Keywords: Ru-Quinoid Carbene • Diazonaphthoquinone • Sulfur ylide • [1,4]-Sigmatropic Shift • Intramolecular concerted S_NAr

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