Organic LETTERS

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Ruthenium Catalyzed Intramolecular C−S Coupling Reactions: Synthetic Scope and Mechanistic Insight

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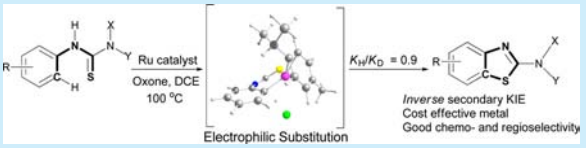
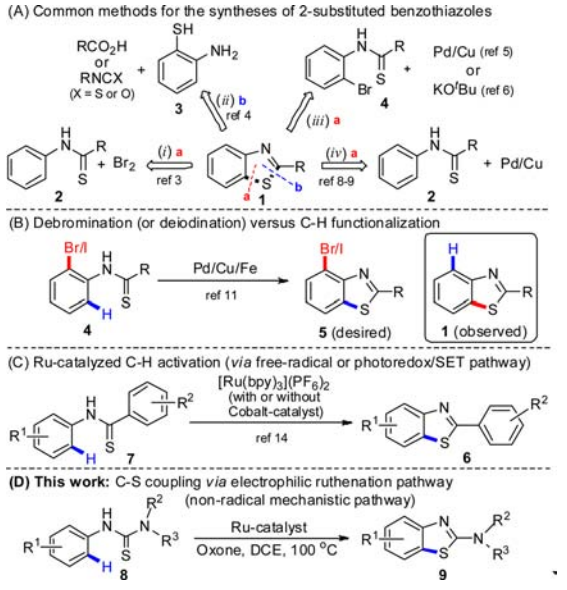
Supporting Information

ABSTRACT: A ruthenium catalyzed intramolecular C−S coupling reaction of *N*-arylthioureas for the synthesis of 2-aminobenzothiazoles has been developed. Kinetic, isotope labeling, and computational studies reveal the involvement of an electrophilic ruthenation pathway instead of a direct C−H activation. Stereoelectronic effect of meta-substituents on the *N*-arylthiourea dictates the final regioselective outcome of the reaction.



Benzothiazole, **1**, is a privileged bicyclic heterocycle that possesses a wide range of applications in medicine[1] and material science.[2] Conventionally, it has been synthesized by intramolecular electrophilic substitution of thiobenzanilides **2** using molecular bromine[3] (Jacobson and Hugerschoff's method, Scheme 1A-*i*), condensation of 2-aminothiophenols **3** with either carboxylic acid or isothiocyanates (Scheme 1A-*ii*),[4] and transition-metal-catalyzed[5] (or strong base mediated[6]) intramolecular C−S bond formation of *ortho*-haloarene precursors **4** (Scheme 1A-*iii*). A recent upsurge in the field of metal-catalyzed C−H bond functionalization[7] has enabled the direct synthesis of benzothiazoles from easily available thiobenzanilides or *N*-phenylthioureas **2** using a Pd-,[8] Cu-,[9] and Fe-catalyst[10] (Scheme 1A-*iv*). Although direct functionalization of an inert C−H bond eliminates dependency on prefunctionalized precursors, these methods based on Pd/Cu/Fe-catalysts generally activate C−H bond chemoselectively with thiobenzamides **4**, where the product **1** is formed exclusively over the desired C−H activated product **5** (Scheme 1B).[11] Since halo-substituted precursors are always preferred under transition-metal-catalyzed C−C/S bond forming reactions,[12] it is essential to explore transition metals other than Pd, Cu, or Fe as catalysts with a different plausible mechanistic discourse, which can directly functionalize the C−H bond chemoselectively (exclusive formation of **5** instead the product **1**). Consequently, cost-effective ruthenium complexes are becoming widely popular in C−H bond activation reactions.[13] Recently, the light-sensitive Ru(II)−polypyridine complex has been employed for the synthesis of 2-substituted benzothiazoles **6** from **7** via C−H functionalization (Scheme 1C).[14] The involvement of radical intermediates in the above-mentioned reactions (via free-radical or photoredox/Single Electron Transfer (SET) pathway) furnished the desired product **6** in poor yields with the substrates containing −Br/−I groups[14b] and failed to produce **6** with the substrates bearing a nitro-group. In our continued quest to generate bioactive heterocycles,[15] herein we report the Ru-catalyzed intramolecular oxidative C−S coupling reactions via an electrophilic ruthenation pathway (nonradical mechanistic pathway) for the synthesis of diversified 2-aminobenzothiazoles **9** (Scheme 1D) with good yields.

Scheme 1. Various Reported Strategies for the Synthesis of 2-Substituted Benzothizoles



We embarked upon our study by examining the conversion of **8a** to **9a** in the presence of various Ru-catalysts and oxidants (Table 1). Initial screening with 10 mol % $RuCl_3$ as the catalyst in the presence of 1 equiv of $Cu(OAc)_2$ as the oxidant in toluene furnished the title compound **9a** in 61% isolated yield (entry 1). Oxone (2 equiv, composed of 50% oxidizing agent $KHSO_5$) was found to be the best among all oxidants studied (entries 1−5)

Received: November 3, 2015
Published: January 13, 2016

DOI: 10.1021/acs.orglett.5b03185
Org. Lett. 2016, 18, 356−359

Table 1. Optimization of Reaction Conditions

entry	catalyst (mol %)/ ligand	oxidant (equiv)	solvent, temp (°C)	time (h)	yield[a] (%)
1	$RuCl_3$ (10)	$Cu(OAc)_2$ (1)	toluene, 110	24	61
2	$RuCl_3$ (10)	$K_2S_2O_8$ (1)	toluene, 110	24	59
3	$RuCl_3$ (10)	$NH_4S_2O_8$ (1)	toluene, 110	24	63
4	$RuCl_3$ (10)	CuI (1)	toluene, 110	24	69
5	$RuCl_3$ (10)	Oxone (2)	toluene, 110	24	80
6	$RuCl_3$ (10)	Oxone (2)	DCE, 100	6	89
7	**$RuCl_3$ (5)**	**Oxone (2)**	**DCE, 100**	**6**	**87**
8	$RuCl_3$ (2.5)	Oxone (2)	DCE, 100	24	80
9	$RuCl_3$ (1)	Oxone (2)	DCE, 100	24	50
10	$RuCl_3$ (5)	Oxone (1)	DCE, 100	6	67
11	–	Oxone (2)	DCE, 100	24	trace
12	$RuCl_3$ (5)	–	DCE, 100	24	race
13	$[RuCp^*Cl_2]_2$[b] (10)	Oxone (2)	DCE, 100	48	37
14	$[RuCl_2(p\text{-cymene})]_2$[b] (5)	Oxone (2)	DCE, 100	6	80

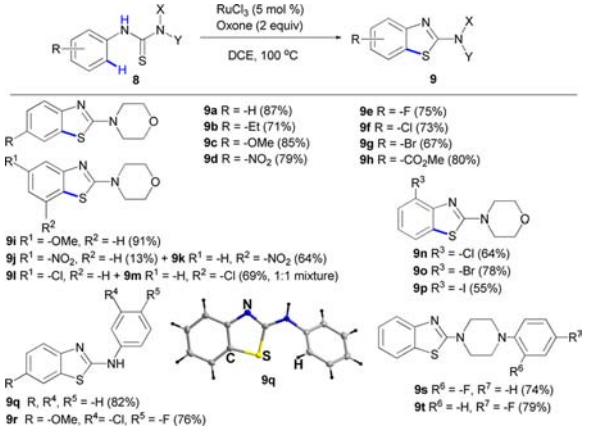
[a]Isolated yield. [b]$AgSbF_6$ was used to activate the catalyst.

with an overall isolated yield of 80% (entry 5). Solvent studies suggest that dichloroethane (DCE) as solvent furnished the product **9a** with maximum yield (89%, entry 6) (see Supporting Information (SI)). The addition of extra ligands such as phosphines, *N*-heterocyclic carbene (NHC), or 2,2′-bipyridine diminished the overall yield of the reactions (see SI). Lowering the catalytic loading from 10 to 5 mol % did not affect the overall outcome of the reaction (entry 7); however, further reduction to 2.5 mol % or less had a detrimental effect on yields (entries 8−9). Employment of either $RuCl_3$ or Oxone alone in the reaction afforded the products in traces (entries 11−12). Similar to $Ru^{III}Cl_3$, $[Ru^{II}Cl_2(p\text{-cymene})]_2$ was found to have equal catalytic activity (entries 7 and 14). In general, optimal reaction conditions included the "$Ru^{II/III}$" catalyst ($Ru^{III}Cl_3$ or $[Ru^{II}Cl_2(p\text{-cymene})]_2$) of 5 mol %, Oxone (2 equiv) in DCE at 100 °C (entry 7).

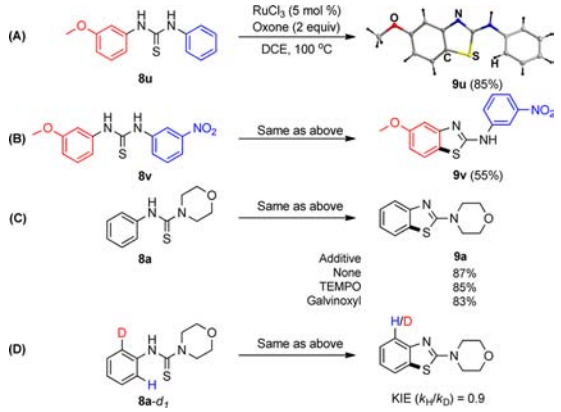
With the optimized reaction conditions in hand, the scope of the current method was investigated using diverse *N*-arylthioureas **8** (Scheme 2). The methodology reported here exhibited broad substrate scope and diversity. Both electron-donating and -withdrawing groups on the phenyl ring of **8** were well tolerated and produced the title compounds **9** in good to excellent yields. It is interesting to note that a substrate with an electron-rich methoxy-group at the *meta*-position proceeded regioselectively to produce **9i** as the only product. In contrast, the presence of an electron-withdrawing nitro-group at the *meta*-position in **8** produced a mixture of **9j** and **9k** in a 1:5 ratio. Whereas, a substrate with the *meta*-chloro substituent produced equal amounts of both regioisomers **9l** and **9m**. In the current context, a particularly appealing feature of the Ru-based catalytic system is the synthesis of 4-halobenzothiazoles **9n−p** without affecting the *ortho*-halide group. On the other hand, the Pd- and/or Cu-based catalytic systems failed to furnish the C−H activated products **9o−p** from the *ortho*-bromo-(or iodo-) phenylthiourea **8** and instead furnished **9a** (Scheme 1B).[8,9,11] Also, the nitro-group on the phenyl ring of **8** was well tolerated in the current catalytic system to furnish **9d** and **9j/k**, which is in contrast to the reported photoredox cyclization using the Ru^{II}−polypyridine complex[14a] that failed to produce **9d**.

During the studies on the scope of the reaction, we observed that an electron-rich *N*-phenylthiourea **8i** (3-OMe) showed higher reactivity than the electron-deficient *N*-phenylthiourea **8j** (3-NO_2) (refer SI). A time-dependent profile of the reactions was obtained by reacting **8i**, **8j**, and unsubstituted substrate **8a** under the optimal reaction conditions. The substrate **8i** exhibited 1.2 and 4.3 times faster reactivity than **8a** and **8j**, respectively. These findings indicate that an electron-rich substituent on the phenyl ring of **8** increases the rate of reaction. To further probe the reaction mechanism, competition experiments were designed to determine if the catalyst would react with either electron-deficient or -rich arenes. Two *N*,*N*′-diphenylthiourea substrates were subjected to the optimized reaction conditions as shown in Scheme 3A, B. In the first instance with **8u**, the catalyst can choose between electron-rich (−C_6H_4-3-OMe) and -neutral (Ph) arenes, and in the second occasion with **8v**, the catalyst can choose between electron-rich (−C_6H_4-3-OMe) and -poor (−C_6H_4-3-NO_2) arenes. In both the cases, cyclization occurred exclusively on the electron-rich phenyl arene to furnish **9u** and **9v** respectively. Thus, both kinetic (refer SI) and competition studies (Scheme 3A, B) suggest that there is a strong preference for an electron-rich phenyl ring over electron-neutral or -poor ones. These data seem to indicate that during the course of the

Scheme 2. Synthesis of 2-Aminobenzothiazole Derivatives (Molecular Structure of 9q Is Shown Separately)



Scheme 3. (A, B) Electron Bias in Ru-Catalyzed Intramolecular C−S Coupling (Molecular Structure of 9u Is Also Shown); (C) Radical Trap Experiments; (D) Kinetic Isotopic Effect Experiment



DOI: 10.1021/acs.orglett.5b03185
Org. Lett. 2016, 18, 356−359

intramolecular C−S coupling, ruthenation of the phenyl ring might have proceeded through an electrophilic substitution process (a nonradical mechanistic pathway).[16] In order to rule out the free-radical mechanistic pathway (or photoredox/SET pathway), we performed the experiments in the presence of free-radical scavengers (TEMPO and Galvinoxyl) and found that the radical scavengers have no effect on the course of the reaction (Scheme 3C). Hence, a nonradical path such as the electrophilic ruthenation[17] is playing a role in the formation of **9**.

We further anticipated that carrying out studies on the kinetic isotopic effect (KIE) could provide valuable information on the mechanistic pathway involving organometallic complexes. Accordingly, we observed an *inverse* secondary KIE (k_H/k_D = 0.9),[18] when isotopically labeled substrate **8a**-d_1 was subjected to the standard reaction conditions (Scheme 3D). The secondary KIE implies that breaking of the C−H bond is not the rate-determining step and is associated with changes in the hybridization state (from sp^2 to sp^3 for *inverse* secondary KIEs) of the arene carbon to which either the proton or deuterium is attached.[19] In general, electrophilic substitution reactions (S_EAr) do not exhibit KIEs[19] and traverse through the transitions state with an sp^3 hybridized arene carbon, called a "σ-complex".[19] The literature precedence indicates that S_EAr is a typical rehybridization process that generally exhibits *inverse* secondary KIEs. On the basis of the kinetic, competition, and isotopic labeling studies, the plausible reaction mechanism based on the electrophilic ruthenation pathway is depicted in Figure 1.[17] The reaction is

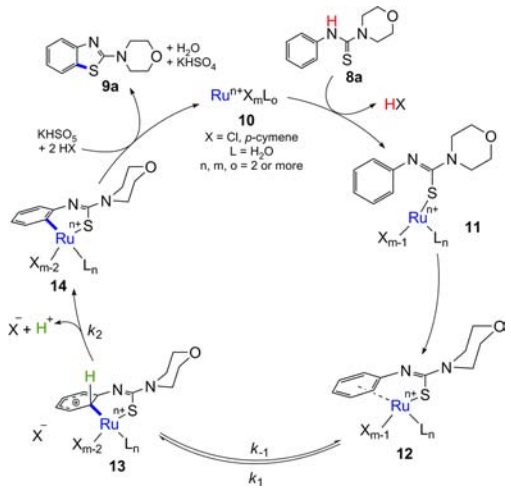


Figure 1. Proposed mechanism.

initiated by coordination of the catalyst **10** with substrate **8a** to form the coordination complex **11** which is transformed to the π-complex **12**. The Ru-center at the π-complex **12** is electrophilically inserted to form the σ-complex **13** which can be converted to the *cyclo*-ruthenated intermediate **14**. According to KIE studies, k_2 is not kinetically significant when compared to k_1; the latter is identified as the rate limiting and reversible step.[20] The reductive elimination of **14** will furnish the title compound **9a**, and the subsequent regeneration of active catalyst **10** by the oxidant will complete the catalytic cycle.

In order to further validate the reaction mechanism, we performed first-principles based theoretical calculations using the hybrid DFT based B3LYP functional.[21] We have started with **11** where the morpholino group was replaced by hydrogen for the simplicity of calculation; the L_n and X were *p*-cymene and Cl, respectively. The equilibrium structure **12** (a π-complex) showed

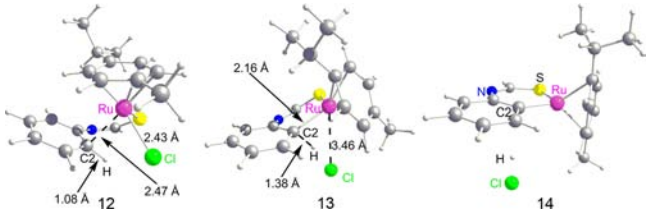


Figure 2. Calculated structures of **12**, **13**, and **14**.

an interaction between Ru and C2 of phenyl with a bond distance of 2.47 Å (Figure 2), and the hydrogen attached to C2 is distorted from planarity by ~17°. When following the reaction mechanism, we found the corresponding transition state where the hybridization of C2 of phenyl has been changed from sp^2 to distorted sp^3 which supports the formation of σ-complex **13** (Figure 2). At the transition state **13**, the Ru−C2 bond distance is further reduced to 2.16 Å with simultaneous lengthening of the C−H (1.38 Å) and Ru−Cl (3.46 Å) bonds (both are about to break with formation of the H−Cl bond). Also, vibrations corresponding to the reaction coordinate clearly show the motion of hydrogen from the C2 to Cl atom and corresponding movement of C2 toward Ru which lead to the distortion of C2 from the planarity of the phenyl ring and hence alteration of hybridization from sp^2 to distorted sp^3. Finally, the ruthenacycle **14** is formed with the elimination of HCl (Figure 2). The strong attractive interaction between C2 and electrophilic Ru^{II} facilitates the breaking of the C−H and Ru−Cl bond which leads to the formation of **14** and HCl.[22] The corresponding energy barrier for this reaction is found to be 26.5 kcal/mol which can be overcome under the optimized reaction conditions (*vide supra*).

The bias for an electron-rich phenyl ring in kinetic and competition studies and the regiochemical outcome of *meta*-substituted analogues can also be rationalized based on the existence of a σ-complex **13**. The cationic charge present in the σ-complex **13** will be effectively stabilized by the presence of an electron-donating substituent (such as −OMe) on the phenyl ring (**8i**, **8u**, and **8v**). In contrast, electron-withdrawing substituents (such as $-NO_2$) on the phenyl ring will destabilize the σ-complex **13**. Hence, electron-rich phenyl rings react faster than electron-deficient ones. The bulky nature of the methoxy-substituent will destabilize the **13a** intermediate, so it favors the formation of the **13b** intermediate, hence leading to the exclusive formation of **9i** (Figure 3).The presence of intramolecular

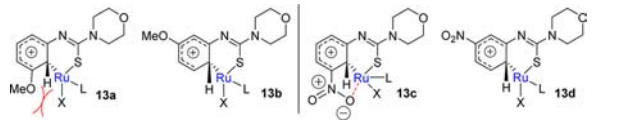


Figure 3. Rational behind regiochemical outcome of 3-OMe- and 3-NO_2-phenylthiourea.

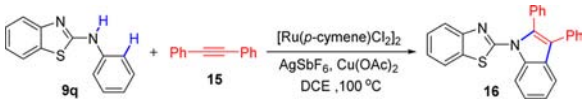
coordinative interaction of the nitro-group with the Ru-center in **13c** will favor formation of **9k** over **9j**. The lack of any such interactions in the case of substrates with a *meta*-chloro substituent leads to equimolar formation of both regioisomers **9l** and **9m**.

We envisaged that the presence of the benzothiazole ring in **9q** could direct the oxidative annulation of alkyne over the aniline side chain.[23] Thus, **9q** was reacted with **15** in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst (Scheme 4). To our delight,

DOI: 10.1021/acs.orglett.5b03185
Org. Lett. 2016, 18, 356−359

it furnished 2-indolylbenzothiazole **16** with 90% isolated yield and **16** is known to possess antiproliferative activity.[24]

Scheme 4. Oxidative Annulation of 9q



In summary, we have developed a new $Ru^{II/III}$-catalyzed C−S coupling of *N*-arylthioureas **8** to produce 2-aminobenzothiazoles **9**. The methodology demonstrated here has broad substrate scope and is expected to find applications in fields such as medicinal chemistry and material sciences. Interestingly, electron-rich substrates exhibited more proficient reactivity than their electron-deficient counterparts. This reactivity indicated the involvement of an electrophilic ruthenation mechanistic pathway which is amply supported by the presence of *inverse* secondary KIE and computational studies. Further studies to explore both the biological activity and photoluminescent characteristics of the benzothiazole compounds are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03185.

Experimental procedures and full characterization of all compounds (PDF)

X-ray crystal structure data for **9q** and **9u** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the help of Dr. Kaisar Raza (Pharmacy, CURAJ) and Pramod Kumar for kinetic studies. We are grateful to CSIR [Grant No. 02(0201)/14/EMR-II] and DST [Grant No. SB/FT/CS-012/2014] for funds and a fellowship to S.S. and R.S.P. respectively.

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(22) The corresponding C−H and Ru−Cl distances in **14** are 2.46 and 4.49 Å respectively, which are considered as broken.

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DOI: 10.1021/acs.orglett.5b03185
Org. Lett. 2016, 18, 356−359