

Unified Gold-Catalyzed Cyclization Approach Towards Isothiazoles from Propargylic Sulfinamides

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Abstract: Isothiazoles are valuable heterocycles in agrochemical and pharmaceutical research, yet they remain synthetically less accessible than their isoxazole counterparts. We report here a gold-catalyzed cyclization of propargylic *N-tert*-butanesulfinamides that provides direct and efficient access to isothiazoles under mild conditions. The transformation proceeds through an unusual cascade: cationic gold activation of the alkyne triggers a 5-endo-dig ring closure with sulfur as the nucleophile followed by irreversible loss of the *tert*-butyl group and dehydrative aromatization. The substrate scope encompasses a range of alkyl and aryl substituents, affording isothiazoles in yields of up to 79%. Reaction monitoring and isolation of key intermediates establish that the cyclic sulfinamide is a direct precursor to the aromatic product and that protic solvents, particularly acetic acid, facilitate the cascade of events, dramatically reducing reaction times. A complementary base-catalyzed pathway from CF₃-substituted substrates selectively delivers cyclic sulfoximines, demonstrating that both heterocyclic classes are accessible from a common precursor by simply switching the activation mode. These results originate from a serendipitous observation made during insecticide research at Syngenta and have broader implications for the design of sulfur-containing heterocyclic scaffolds.

Keywords: Gold catalysis · Isothiazole · Propargylic sulfinamide



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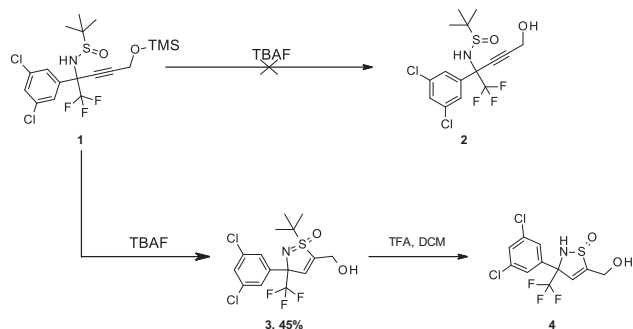
Medical Research Council – National Institute for Medical Research (Mill Hill, London; 2005–2008) and University College London (2008–2011) before joining Syngenta in 2011 at Jealott's Hill International Research Centre (UK), where he is a member of the Structural Biology group.

1. Introduction

Isothiazoles have been known as bioisosteric replacements for isoxazoles in both pharmaceutical and agrochemical programs for many years.^[1] They remain, however, somewhat less accessible synthetically: a Scifinder® search carried out in 2025 indicated that there are roughly seven times fewer reported preparations of isothiazoles than of isoxazoles. We describe here how, starting from a serendipitous observation, we developed a gold-catalyzed cyclization of propargylic *N-tert*-butanesulfinamides that delivers isothiazoles through an unusual three-steps sequence: 5-endo-dig ring closure with sulfur as the nucleophile, loss of the *tert*-butyl group, and dehydrative aromatization.

2. First Results

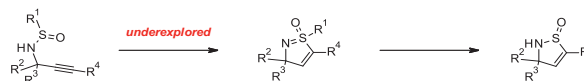
As part of a long-standing insecticide research project in our team, we explored a broad family of five-membered nitrogen-containing heterocycles bearing a trifluoromethyl (CF₃) group. This work ultimately contributed to the discovery and development of PLINAZOLIN® technology, a new product now commercialized by Syngenta. In the course of expanding the chemical space around these CF₃-substituted heterocycles, we prepared a series of functionalized intermediates targeting novel structural variants. Among these, the reactivity of a particular propargyl sulfinamide intermediate **1** attracted our attention beyond its intended role as a building block in our project (Scheme 1). Indeed, when compound **1** was subjected to tetrabutylammonium fluoride (TBAF) conditions in order to deprotect the silylated group on the oxygen and obtain the compound **2**, a spontaneous cyclization occurred and the cyclic sulfoximine **3** was isolated as the major compound of the reaction. Intrigued by this new heterocycle, we thought we could also attempt to remove the *tert*-butyl group, so we treated sulfoximine **3** with trifluoroacetic acid, which yielded the cyclic sulfinamide **4** as the major compound.



Scheme 1. Serendipitous discovery: TBAF-mediated cyclization of CF₃-substituted propargylic sulfinamide.

At that time, the preparation of both these cyclic sulfoximines and cyclic sulfinamides was rather scarce in the literature,^[2] so we decided to embark on a project to evaluate the scope and limitations of this chemical transformation, as described in Scheme 2.

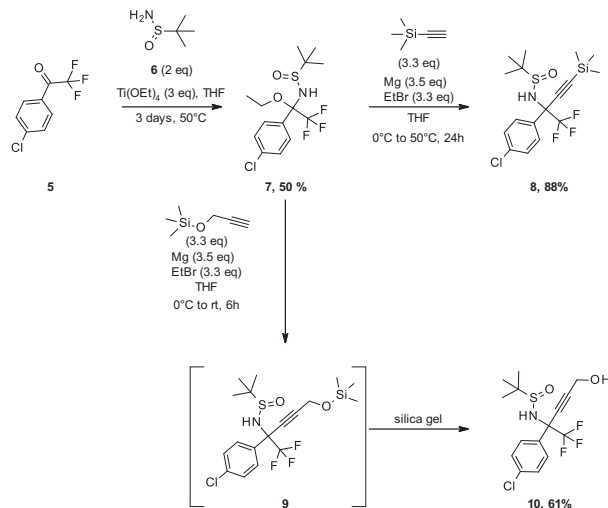
Here we report the preparation and reactivity of these intermediates, which revealed unexpected chemistry with broader synthetic implications.



Scheme 2. Proposed investigation of the scope and limitations for the cyclization of propargylic sulfinamides.

2.1 Substrate Preparation

The starting propargylic sulfinamides were assembled in two steps starting from racemic *N-tert*-butanesulfinamides (Scheme 3). In the case of trifluoromethyl ketones as the starting material, the sulfinyl imines were not isolated. Indeed, as perfluoroalkyl groups adjacent to imines are known to increase their reactivity toward nucleophiles and to have a stabilizing effect on the obtained quaternary species, the *N*-sulfinyl hemiaminals were instead isolated, as highly stable and as a mixture of diastereoisomers. Of note, the condensation reaction with *N-tert*-butanesulfinamides worked best in our hands using Ti(OEt)₄ instead of Ti(OiPr)₄ as a Lewis acid.^[3] Adding an organomagnesium or organolithium acetylide to trifluoromethyl ketone-derived *N*-sulfinyl hemiaminals gave the propargylic sulfinamides as single major diastereomers. The addition of the reagent presumably occurs on the intermediate ketoimine and thus the separation of both diastereoisomers of hemiaminals from the first step was unnecessary for this reaction. The diastereoselectivity of the addition fits a Zimmerman–Traxler 6-membered chair-like transition state model in which the CF₃ group sits equatorial, away from the sulfur lone pair. This was indeed confirmed by X-ray diffraction analysis of one analog (see supplementary information).



Scheme 3. Two-step synthesis of propargylic sulfinamide substrates.

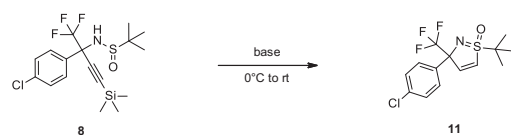
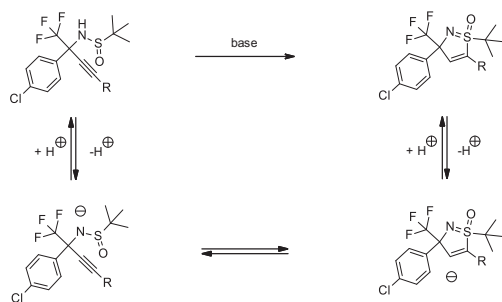
2.2 Base-Catalyzed Cycloisomerization: Cyclic Sulfoximines

We initially examined base-mediated cyclization conditions on the CF₃-substituted substrate **8** (Scheme 4). These reactions consistently furnished the desired cyclic sulfoximine **11** in good yields and short reaction times (Table 1). TBAF (1 equiv.) in ethyl acetate was the fastest system, giving 88% yield in 15 minutes; NaOMe/MeOH was nearly as good (86%). Even 0.1 equiv. of TBAF still returned >80%, confirming that the transformation proceeds catalytically.

Mechanistically, the ring closure is most probably a 5-endo-dig process: the sulfur lone pair attacks the triple bond, assisted by the α -effect of the deprotonated nitrogen, and proton transfer from N to the resulting vinyl carbanion provides the cyclic sulf-

Table 1. Base-catalyzed cycloisomerization of CF₃-substituted propargylic sulfonamide **8**.

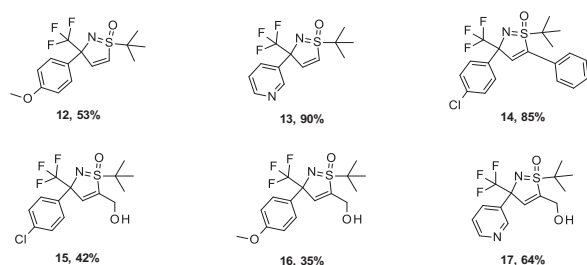
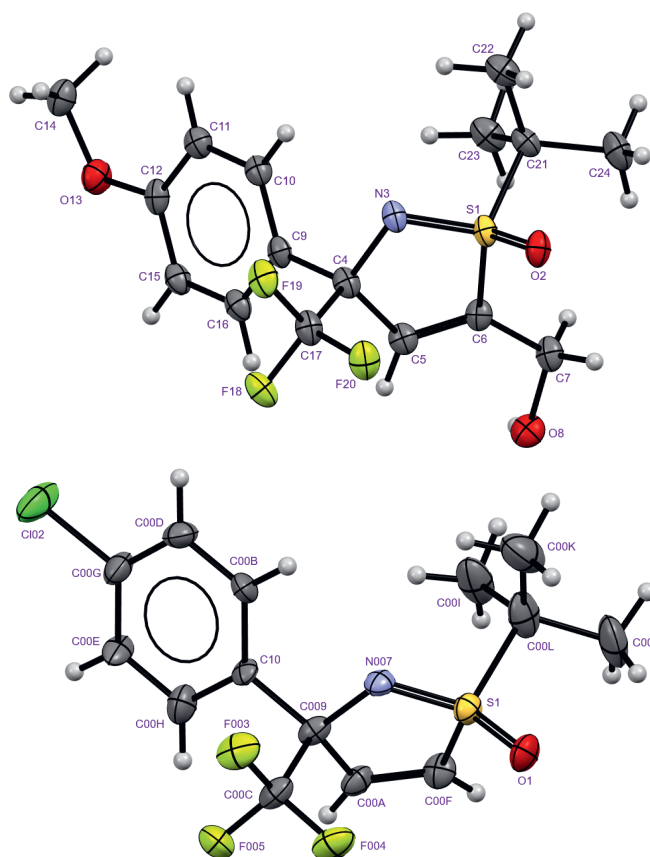
Base	Solvent	Time	11 yield (%)
TBAF (1 eq)	EtOAc	15 min	88
NaOMe	MeOH	30 min	86
NaH	DMF	30 min	69
KOtBu	THF	20 min	64
TBAF (0.1 eq)	EtOAc	15 min	>80

Scheme 4. Base-catalyzed 5-endo-dig cycloisomerization of CF₃-substituted propargylic sulfonamide.

Scheme 5. Proposed mechanism for the base-catalyzed 5-endo-dig cycloisomerization to cyclic sulfoximines.

oximine, as shown in Scheme 5. Presumably the trifluoromethyl group helps in at least three ways – it lowers the NH pK_a, increases the triple-bond electrophilicity, and introduces a Thorpe–Ingold compression that pre-organizes the chain for cyclization, thus enabling a fast cyclization.

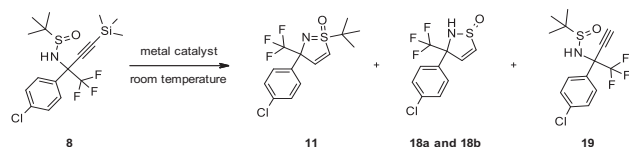
Next, a few more substrates were evaluated, and it was found that various alkyl groups at the propargylic position were well tolerated (Fig. 1). Notably, every substrate examined gave a single diastereomer during these reactions. Based on the X-ray crystal structure of a few analogs, it was found that the sulfur–carbon bond formation occurs with retention of configuration at sulfur (Fig. 2).

Fig. 1. Scope of the base-catalyzed cycloisomerization of CF₃-substituted propargylic sulfonamide.Fig. 2. ORTEP representations of [1-*tert*-butyl-3-(4-methoxyphenyl)-1-oxo-3-(trifluoromethyl)isothiazol-5-yl]methanol (upper) and 1-*tert*-butyl-3-(4-chlorophenyl)-3-(trifluoromethyl)isothiazole 1-oxide (lower) with thermal ellipsoids shown at the 50% probability level. Hydrogen atoms of arbitrary size.

2.3 Metal-Catalyzed Cyclization: Discovery of the Isothiazole Pathway

The 2010s saw a surge in homogeneous gold catalysis – a period referred to as the ‘gold rush’ – driven by gold’s exceptional ability to activate unsaturated C–C bonds toward nucleophilic attack. Among the most extensively studied transformations are intramolecular cyclizations proceeding *via* activation of alkynes toward heteroatom nucleophiles. While oxygen and nitrogen nucleophiles have been widely explored in this context, examples involving sulfur nucleophiles remain comparatively scarce. This disparity likely reflects the well-known tendency of organosulfur compounds – thiols, sulfides, and disulfides – to coordinate strongly to transition metals, and to gold in particular, raising concerns about catalyst inhibition in the presence of these functional groups.^[4] We nevertheless embarked on a study and evaluated silver or gold catalysis on our substrates. A fundamentally different outcome was observed under these metal-catalyzed conditions. When CF₃-containing substrate **8** was treated with silver or gold catalysts, the isomeric unsaturated cyclic sulfinamides **18a** and **18b** were isolated instead of cyclic sulfoximine **11**, with concomitant loss of the *tert*-butyl group (Scheme 6 and Table 2). This was achieved using either AgOTf, AgSbF₆ or the combination of Au(PPh₃)Cl + AgSbF₆ in ethanol as the preferred solvent. In contrast, AgBF₄ in ethanol delivered the byproduct **19** in 80% yield.^[4] From the few reaction conditions tested, AgSbF₆ in ethanol proved best to afford one of the diastereomeric cyclic sulfinamide pair **18** in 82% yield.

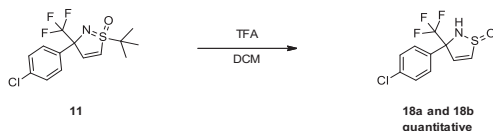
In order to understand if the cyclic sulfinamides **18** could derive from cyclic sulfoximine **11** during the reaction, the cyclic sulfoximine **11** was treated with trifluoroacetic acid. As mentioned before on a related substrate, these acidic conditions pro-

Scheme 6. Metal-catalyzed cyclization of CF₃-substituted substrate **8**.Table 2. Metal-catalyzed cyclization of CF₃-substituted substrate **8**.

Catalyst	Solvent	18a and 18b yield (%)	19 yield (%)
AgOTf	EtOH	10 / 71	-
AgSbF ₆	EtOH	- / 82	-
AgBF ₄	EtOH	-	80
AgBF ₄	DCM	39 / 18	-
Au(PPh ₃)Cl + AgSbF ₆	EtOH	13 / 58	6
Au(PPh ₃)Cl + AgSbF ₆	DCM	10 / 23	-

vided the cyclic sulfinamide **18** in high yield (Scheme 7). This result suggests why the cyclic sulfinamide **18** is not observed during the silver or gold catalyzed reaction, as the loss of *tert*-butyl group from cyclic sulfoximine **11** is probably irreversible and this could drive the equilibrium towards the cyclic sulfinamide **18**.

These results are particularly noteworthy for two reasons. First, this approach provides access to compounds not previously described in the literature. Second, the metal-catalyzed reaction proceeds successfully with an unusual sulfur nucleophile adding across a triple bond. Notably, the silver or gold catalyst retains activity in the presence of both substrate and products, showing no significant deactivation. Furthermore, we observe selective sulfur cyclization despite the sulfinamide oxygen representing a viable competing nucleophile – a pathway that would lead to a 6-endo-dig cyclization, as documented in the literature for structurally related sulfoxides.^[5] This chemoselectivity for sulfur over oxygen addition is a rare outcome and warrants further mechanistic investigation.

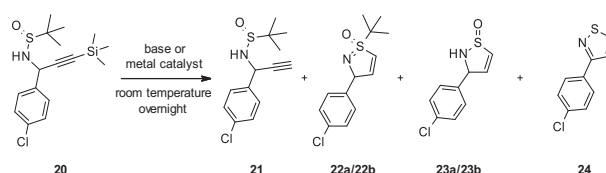
Scheme 7. Acid-mediated conversion of cyclic sulfoximine **11** to cyclic sulfinamide **18**.

Eventually, it is worth noting that the reaction outcome from CF₃-substituted propargylic sulfinamides is strongly dependent on conditions: under basic conditions, the cyclization delivers cyclic sulfoximines, whereas metal catalysis selectively directs the reaction toward cyclic sulfinamides. This divergence demonstrates that the two pathways can be controlled independently, offering synthetic access to both heterocyclic classes from a common substrate.

3. Scope Expansion

3.1 First Results with Aldimines

To determine whether the reaction would proceed in the absence of the CF₃ group, we next turned our attention to aldimine-

Scheme 8. Gold/silver-catalyzed cyclization of aldimine-derived substrate **20**.

derived precursors. The substrates were prepared in a similar manner using an organolithium acetylide addition on aldimines.

The failure of the previously successful basic conditions (TBAF or NaOMe) to trigger any cyclization with substrate **20** confirmed the specific role of the CF₃ group for the activation of the earlier substrates towards the cyclization.

However, under the previously metal-catalyzed conditions using aldimine-derived substrate **20**, the isothiazole **24** appeared in the product mixture alongside the cyclic sulfinamides **23a/23b**, with no cyclic sulfoximines **22a/22b** detected as before under silver or gold catalysis (Scheme 8). The reaction monitoring indicated that the cyclic sulfinamides **23a/23b** serve as precursors to the isothiazole **24**, most probably through a dehydration process.

The Au(PPh₃)Cl/AgSbF₆ combination in DCM provided the best initial result (52% cyclic sulfinamides **23a/23b**, 33% isothiazole **24**, see Table 3).

Table 3. Metal-catalyzed cyclization of substrate **20**.

Catalyst	Solvent	21 yield (%)	23a/23b yield (%)	24 yield (%)
AgSbF ₆	DCM	–	19	18
AgSbF ₆	EtOH	–	34	22
AgOTf	EtOH	26	32	11
AgOTf	DCM	–	27*	17*
Au(PPh ₃)Cl + AgSbF ₆	DCM	–	52	33

*Yield after recrystallization

In addition, the X-ray diffraction of the cyclic sulfinamides **23a/23b** revealed an almost planar ring system with the nitrogen adopting near-sp² hybridization and the lone pair on the nitrogen being coplanar with the S=O bond (Fig. 3).

Subsequently, some further tests on analogs revealed that in the case of substrates bearing more hindered alkynes, such as **25** and **26**, a possible competing pathway could be observed, with the sulfoxide oxygen addition on the triple bond instead of the sulfur (5-endo-dig cyclization from S nucleophile versus 6-endo-dig cyclization from oxygen nucleophile), leading to the imines **30** and **31** (Scheme 9). With substrate **25** it was also possible to isolate the cyclic sulfoximine **27a**, obtained as 1 diastereoisomer mainly.

Eventually, the formation of isothiazoles directly from propargylic sulfinamides in a single operational step was particularly exciting. Indeed, through a cascade of events – Ag/Au-catalyzed 5-endo-dig cyclization, preferential sulfur addition onto the activated triple bond, loss of the *tert*-butyl group, and final dehydrative aromatization – this transformation converts readily available precursors directly into a heterocyclic scaffold that remains synthetically challenging to prepare by other means. This prompted us to further optimize the reaction conditions towards the isothiazole formation.

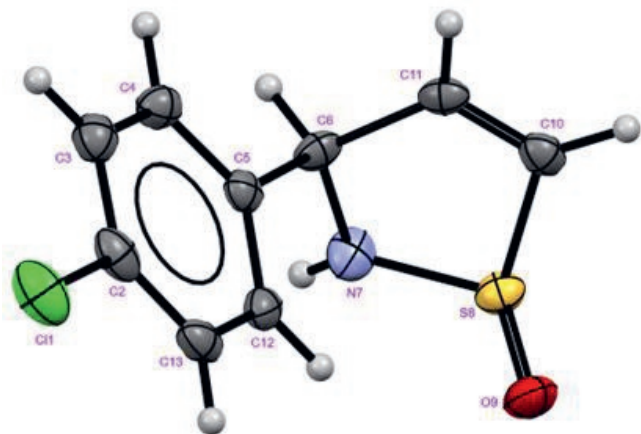
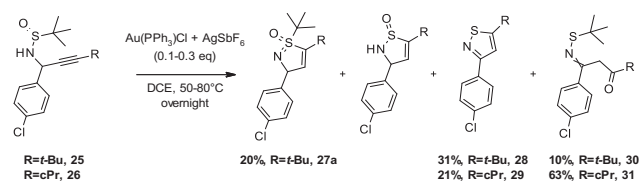


Fig. 3. ORTEP representation of 3-(4-chlorophenyl)-2,3-dihydroisothiazole 1-oxide with thermal ellipsoids shown at the 50% probability level. Hydrogen atoms of arbitrary size.



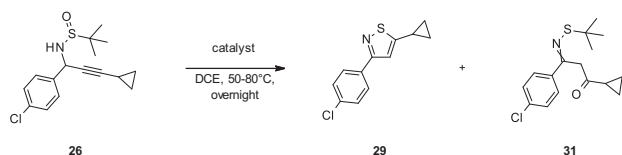
Scheme 9. Competing 5-endo-dig (sulfur) vs. 6-endo-dig (oxygen) cyclization pathways.

3.2 Optimization of the Gold-Catalyzed Isothiazole Synthesis

Starting from the difficult substrate **26**, we screened a series of gold catalysts with different ligand electronics – electron-poor (tris(4-(trifluoromethyl)phenyl)phosphine), electron-rich (IMes NHC), sterically demanding (JohnPhos, XPhos) – but none afforded a significant improvement in isothiazole **29** yield over the standard Au(PPh₃)Cl/AgSbF₆ system (Scheme 10 and Table 4).

In contrast, solvent optimization proved far more impactful on substrate **20** (Scheme 11 and Table 5). Moving from DCM (33%) to more polar solvents substantially improved yields: ethanol (69%) and THF (72%) were both effective. Acetic acid was an interesting case: the yield was moderate (53%), but the reaction was noticeably cleaner and finished within 30 minutes instead of a full day.

Control experiments confirmed that neither AcOH alone, AgSbF₆ in AcOH, nor Au(PPh₃)Cl in AcOH promoted cyclization at 80 °C, establishing that both the gold catalyst and the silver co-catalyst are essential. The beneficial role of acetic acid is attributed to its ability to facilitate all proton-requiring steps in the mechanism: protodemetalation, the loss of the *tert*-butyl group, and dehydrative aromatization to the isothiazole. THF presumably coordinates to the cationic gold center and attenuates its Lewis acidity, the higher polarity of THF likely compensates by stabilizing charge separation that accompanies gold activation of the alkyne.

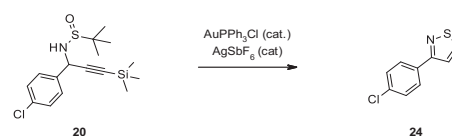


Scheme 10. Gold catalyst ligand screen for the cyclization of substrate **26**.

Table 4. Metal-catalyzed cyclization of substrate **26**: catalyst screen

Catalyst (0.1-0.3 eq)	29 yield (%)	31 yield (%)
Au(PPh ₃)Cl + AgSbF ₆	21	63
Au((<i>p</i> -CF ₃ Ph) ₃ P)Cl + AgOTf	-	51
Au((<i>p</i> -CF ₃ Ph) ₃ P)Cl + AgSbF ₆	detected*	detected*
Au(IMes)Cl + AgOTf	detected*	detected*
Au(IMes)Cl + AgSbF ₆	detected*	detected*
JohnPhos Au(MeCN)SbF ₆	12	48
XPhosAuNTf ₂	18	21

*messy reaction



Scheme 11. Solvent optimization for the gold-catalyzed isothiazole synthesis from substrate **20**.

Table 5. Solvent influence on the gold-catalyzed isothiazole synthesis.

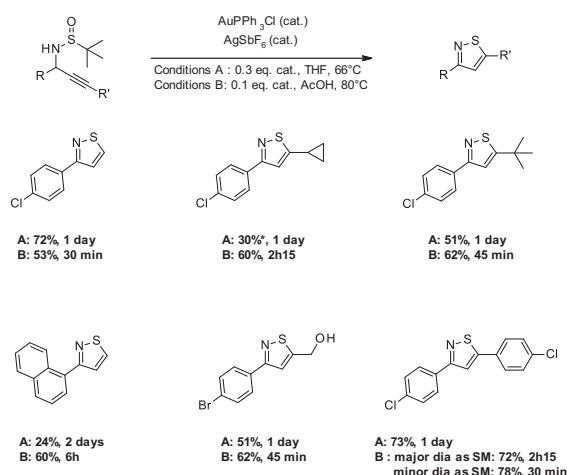
Solvent	Conditions	Reaction time	24 yield (%)
DCM	0.1 eq cat., rt	24h	33
ClPh	0.2 eq cat., 80 °C	24h	37
Ethanol	0.2 eq cat., 78 °C	24h	69
THF	0.2 eq cat., 66 °C	24h	72
Acetic acid	0.1 eq cat., 80 °C	30 min	53

3.3 Substrate Scope

We applied the two best sets of conditions (0.3 equiv. catalyst in THF at 66 °C, or 0.1 equiv. catalyst in AcOH at 80 °C) to a range of substrates (Scheme 12). Cyclopropyl, *n*-butyl, TMS-protected alkynyl, aryl, and even unsubstituted terminal alkynes all cyclized, giving isothiazoles in 24–79% yield. In almost all cases, acetic acid outperformed THF. Substrates bearing *ortho*-substituents on the aryl ring or bulky R' groups reacted more slowly, likely due to the increased steric hindrance near the reactive site. In the case where R' was *p*-chlorophenyl, both diastereomers of the starting material underwent cyclization successfully: the major diastereomer afforded 72% and the minor 78% yield in AcOH. A reactivity difference between these diastereomers was observed, possibly due to differential coordination of gold to the sulfur center.^[5a]

3.4 Mechanistic Proposal

Based on the experimental observations – isolation of intermediates, X-ray structures, control experiments, and reaction monitoring – we propose the following mechanism for the gold-catalyzed isothiazole formation:



Scheme 12. Substrate scope of the gold-catalyzed isothiazole synthesis.

Alkyne activation: The cationic gold species coordinates to the triple bond, enhancing its electrophilicity toward intramolecular nucleophilic attack.

5-endo-dig cyclization: The sulfur lone pair attacks the activated alkyne. Sulfur is preferred over the sulfinamide oxygen as the nucleophile, which would have led to a 6-endo-dig cyclization product as reported for sulfoxide substrates. This chemoselectivity is one of the distinguishing features of the present transformation.

Protodemetalation and *tert*-butyl loss: Protonation of the C–Au bond regenerates the catalyst. The irreversible loss of the *tert*-butyl group drives the equilibrium forward and the nitrogen lone pair forms the N=S double bond characteristic of the cyclic sulfinamide intermediate.

Aromatization: Dehydration of the cyclic sulfinamide intermediate provides the fully aromatic isothiazole product. This final step is facilitated by protic solvents such as acetic acid, explaining the shorter reaction times observed under acidic conditions.

In the case of sterically demanding substrates and less protic solvents, a competing 6-endo-dig pathway can occur, arising from the intramolecular oxygen attack on the activated alkyne leading to the oxo derivative after hydrolysis.

4. Conclusions

We have developed an unprecedented gold-catalyzed transformation of unactivated propargylic *N-tert*-butanesulfinamides into isothiazoles. The method offers several notable features over literature precedents: (i) the substrates are not particularly activated alkynes and are easily prepared in two steps from commercial sulfinamide reagents; (ii) the reaction proceeds under mild conditions with moderate gold catalyst loadings; (iii) a range of alkyl and aryl substituents are tolerated, affording isothiazoles in yields of up to 79%; This gold-catalyzed pathway expands the synthetic utility of propargylic sulfinamides and the synthetic toolbox for isothiazole construction – a heterocyclic class of importance in crop protection and pharmaceutical research.

Acknowledgements

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- [2] Related reactions published since 2013: (a) X.-N. Wang, R. P. Hsung, R. Qi, S. K. Fox, M.-C. Lv, *Org. Lett.* **2013**, *15*, 2514, <https://doi.org/10.1021/ol400989x>; (b) X.-N. Wang, R. P. Hsung, S. K. Fox, M.-C. Lv, R. Qi, *Heterocycles* **2014**, *88*, 1233, [https://doi.org/10.3987/COM-13-S\(S\)88](https://doi.org/10.3987/COM-13-S(S)88); (c) P. Cividino, C. Verrier, C. Philouze, S. Carret, J.-F. Poisson, *Adv. Synth. Catal.* **2019**, *361*, 1236, <https://doi.org/10.1002/adsc.201801408>; (d) Y. Aota, Y. Maeda, T. Kano, K. Maruoka, *Chem. Eur. J.* **2019**, *25*, 15755, <https://doi.org/10.1002/chem.201904501>; (e) Y. Chang, C. Xie, H. Liu, S. Huang, P. Wang, W. Qin, H. Yan, *Nat. Commun.* **2022**, *13*, 1933, <https://doi.org/10.1038/s41467-022-29557-1>; (f) Z. Li, N. Wang, J. Liu, H. Mei, V. A. Soloshonok, J. Han, *Org. Lett.* **2021**, *23*, 6941, <https://doi.org/10.1021/acs.orglett.1c02538>.
- [3] More studies on the diastereoselective addition of organomagnesium and organolithium reagents to chiral trifluoromethyl *N-tert*-butanesulfinyl hemiaminals, see: F. Grellopis, A. B. Jamaa, A. Gassama, *Eur. J. Org. Chem.* **2013**, *29*, 6694, <https://doi.org/10.1002/ejoc.201300890>.
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- [5] (a) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160, <https://doi.org/10.1021/ja070789e>; (b) G. Li, L. Zhang, *Angew. Chem. Int. Ed.* **2007**, *46*, 5156, <https://doi.org/10.1002/anie.200701449>; (c) A. B. Cuenca, S. Montserrat, K. M. Hossain, G. Mancha, A. Lledós, M. Medio-Simón, G. Ujaque, G. Asensio, *Org. Lett.* **2009**, *11*, 4906, <https://doi.org/10.1021/ol9020578>; (d) L. Ye, W. He, L. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 3236, <https://doi.org/10.1002/anie.201007624>.

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