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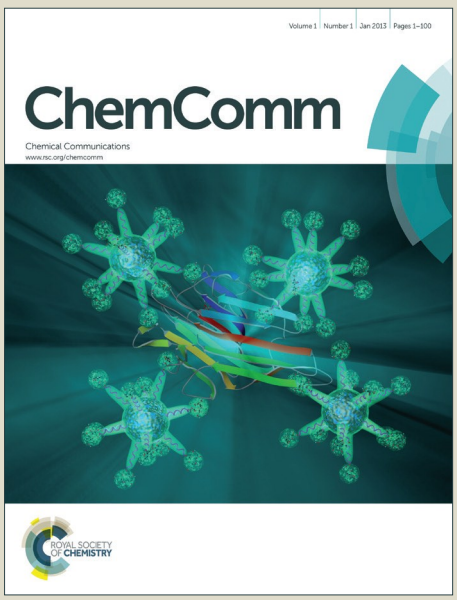

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Asymmetric Alkynylation/Hydrothiolation Cascade: Enantioselective Synthesis of Thiazolidine-2-imines from Imine, Acetylene and Isothiocyanate

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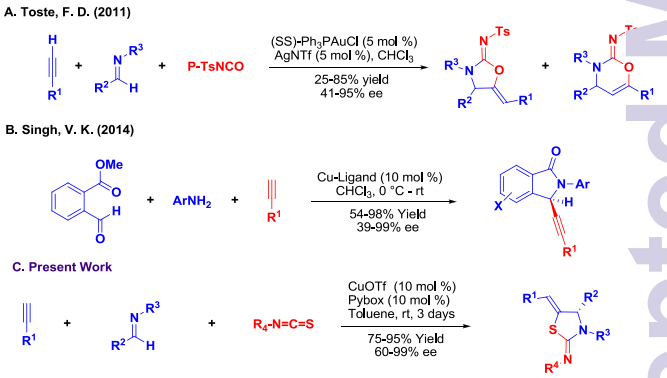
Alok Ranjan,[a] Anupam Mandal,[a] Swapnil G. Yerande,[b] Dattatraya H. Dethe,*[a]

Multicomponent reaction amongst imine, terminal alkyne, and isothiocyanate in presence of catalytic chiral copper-pybox complex proceedes enantioselectively to give enantiopure thiazolidine-2-imine (60-99% *ee*) by highly regioselective intramolecular 5-*exo-dig* hydrothiolation reaction.

Azolines are five membered nitrogen atom containing heterocycles belonging to many natural products and pharmaceuticals.[1] In addition; many enantiopure azolidine derivatives have received attention due to their application as a synthetic intermediates, auxiliaries, ligands and catalysts for asymmetric synthesis. Various thiazolidines exhibit anti-inflammatory,[2] antiviral,[3] anticonvulsant and cardiovascular properties.[4] In 2013 Punniyamurthy and Sengoden[5] reported the on water iron catalysed cycloaddition of aziridines with heterocummules for the synthesis of azolidines in racemic form. In 2007 Kwon and coworkers[6] reported an elegant asymmetric synthesis of azoline derivatives using bisphosphine-catalyzed mixed double-Michael reactions. Despite these advances for synthesis of azoline derivatives, methods for enantioselective synthesis of thiazolidine derivatives, are scarce.

In 2011 Toste *et al.* reported a beautiful monophosphine gold (I) catalyzed enantioselective synthesis of oxazolidines by multicomponent one pot transformation (Scheme 1A).[7] Singh *et. al.* reported an unprecedented Cu(I)–pybox-diPh-catalyzed highly enantioselective alkynylation/lactamization cascade (up to > 99% *ee*) (Scheme 1B) for the synthesis of diversely substituted isoindolinones and tetrahydroisoquinoline.[8] Besides drawing inspiration from the work of Toste *et al.*[7] and Singh *et. al.*[8] we also took a clue from our recently reported synthesis of imidazolidine-2-thione through base catalyzed intramolecular 5-*exo-dig* hydroamination of the



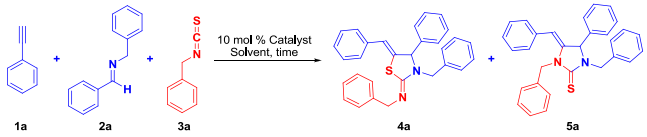
Scheme 1 Current state of the art and proposed asymmetric alkynylation/hydrothiolation cascade.

propargylthiourea.[9] It was envisioned that the enantiopure thiazolidine-2-imine can also be synthesised by an asymmetric alkynylation/hydrothiolation cascade from imine, acetylene and isothiocyanate (Scheme 1C). We hypothesized that in this multicomponent reaction first the alkyne will add on to the chiral copper-pybox catalyst activated iminium ion to generate propargylamine *in situ,* the propargylamine thus formed will react with isothiocyanate in addition/intramolecular hydrothiolation sequence where isothiocyanate will play a dual role as an electrophile and nucleophile to construct thiazolidine-2-imine.

We started our investigation by optimizing conditions for the one-pot preparation of racemic thiazolidine-2-imine **4**. In a typical experiment, solvent (3 mL), imine **2a** (0.50 mmol), phenyl acetylene 1**a** (0.65 mmol), benzyl isothiocyanate **3a** (0.55 mmol) and catalyst (10 mol %) were combined in a 20 mL vial at room temperature (30 °C) equipped with a magnetic stir bar and a screw cap. The resultant mixture was stirred at room temperature for 12 h. When this reaction was carried out using 10 mol % triflic acid, the reaction proceeded smoothly to provide the corresponding hydrothiolation product **4a,** albeit in 45% yield. Surprisingly hydroamination product **5a** was not observed (Table 1, entry 1). When the solvent was changed from toluene to dichloromethane yield of **4a** improved up to

[a] *Department of Chemistry, Indian Institute of Technology Kanpur-208016, Uttar Pradesh, India.*
[b] *Acoris Research (A Division of Hikal Ltd). 3A, International Biotech Park, Hinjewadi, Pune 411 057, Maharashtra, India.*
[c] *Electronic supplementary information (ESI) available: Experimental procedures and characterization of all new compounds. For ESI and crystallographic data in*

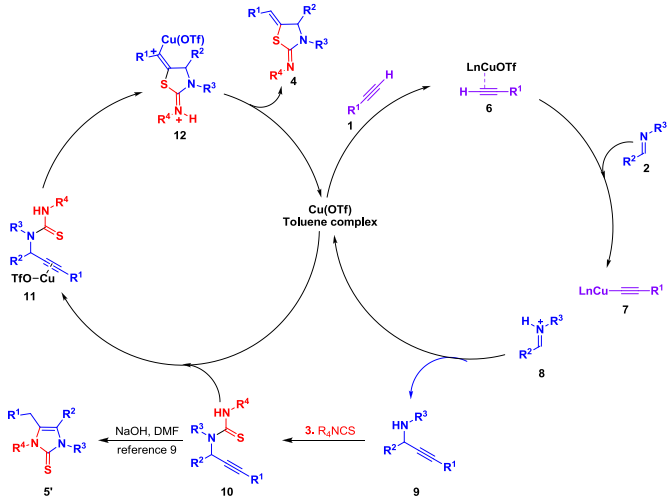
Table 1 Optimization of Reaction Conditions for the One Pot Formation of Thiazolidine-2-iminea



Entrya	Catalyst (10 mol %)	Solvent	% Yieldb **4a**	% Yieldb **5a**
1	Triflic acid	Toluene	45	
2	$FeCl_3$	Toluene	50	
3	Triflic acid	CH_2Cl_2	70	
4	$FeCl_3$	EtOAc	40	
5	$FeCl_3$	CH_2Cl_2	74	
6	$Cu(OTf)_2$	CH_2Cl_2	70	25
7	$Rh(OAc)_2$	CH_2Cl_2	55	35
8	$Cu(OTf)_2$	Toluene	85	10
9	$In(OTf)_3$	CH_2Cl_2	58	
10	$Fe(OTf)_3$	CH_2Cl_2	73	
11	CuI	CH_2Cl_2	40	
12	CuOTf	Toluene	90	

[a] All the reactions were performed with imine (0.50 mmol), acetylene (0.65 mmol) and isothiocyanate (0.55 mmol), 10 mol % catalyst, solvent (3 mL) for 12 h at 30 °C .[b]Isolated yield after column chromatography.

70% (Table 1, entry 3). Desired product **4a** was also formed in moderate yield when 10 mol % $FeCl_3$ was used as a catalyst (Table-1 entries 2, 4 and 5). Conversely, we detected the formation of the hydroamination product **5a** along with the hydrothiolation product **4a** when 10 mol % of $Cu(OTf)_2$ and $Rh(OAc)_2$ (Table 1, entries 6-8) were used. Lewis acid $In(OTf)_3$ and $Fe(OTf)_3$ were found proficient in carrying out this transformation (Table 1 entries 9 and 10). Compound **4a** was formed in only 40% yield when copper iodide was used as a catalyst (Table 1, entry 11). After screening various solvent and catalyst combinations, it was found that the use of CuOTf toluene complex and toluene as a solvent leads to the exclusive formation of **4a**.



Scheme 2 Tentative Mechanism of Multicomponent Reaction

The 90% yield obtained of **4a** using CuOTf toluene is a marked improvement compared to yield obtained when CuI was used as a catalyst (Table 1, entry 12 *vs.* entry 11). The plausible mechanism for this multicomponent reaction depicted in Scheme 2. Initial coordination of Cu with alkyne forms the π-complex **6**, further complexation of **6** with imine **2** provides the complex **7**, and deprotonation by imine produces copper acetylide with a coordinated iminium ion. An addition reaction leads to propargylamine **9** and regenerates the copper catalyst. Propargylamine **9** is then trapped with isothiocyanate to generate propargylthiourea **10**; the alkyne then coordinates with copper to form the second π-alkyne complex **11**. 5-*exo-dig* cyclization by nucleophilic attack of the thiourea sulphur (hydrothiolation) forms the product and regenerates the copper catalyst.

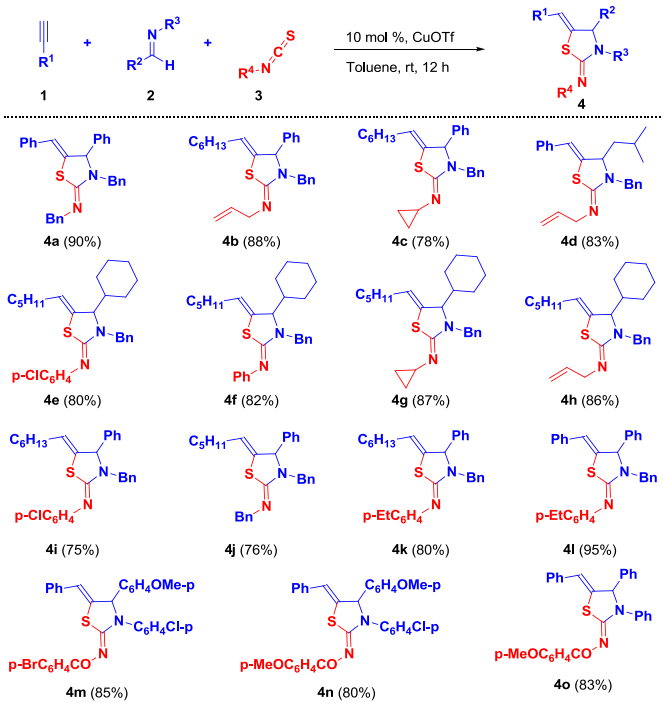
Many points about this multicomponent atom economical transformation are worthy of mention. First cyclization step generated only the five member thiazolidine product **4** in highly regioselective fashion through 5-*exo-dig* cyclization, we did not observe the 6-*endo-dig* cyclization product under the optimized condition. Prior to this work we have reported base catalyzed hydroamination reaction for the construction of imidazolidine-2-thione **5** from propargylthiourea **10** by 5-*exo-dig* cyclization through nucleophilic attack of the thiourea nitrogen.[9] In the present investigations using CuOTf as a catalyst thiazolidine-2-imine **4** was formed exclusively and formation of 5-exo-dig hydroamination product **5**, and 6-endo-dig hydroamination product were not observed at all. We believe that under this optimized reaction condition, *in situ* formed propargylthiourea **10** exist in a thiol tautomeric form, the resultant more nucleophilic sulphur attacks the activated alkyne resulting in the exclusive formation of thiazolidine-2-imine **4.**

Having achieved a proof of concept for our proposed hypothesis, we turned our attention to test the scope of the established protocol. To this end a small library of thiazolidine-2-imine **4** were synthesized and the results obtained are summarized in Table 2. Gratifyingly, the reaction was proved to be very general under the optimized conditions, performing well in all of the cases examined. At first, the scope of the reaction with various alkynes was studied. The aromatic alkynes reacted well with variety of imines and isothiocyanate under this condition to afford products **4a-4o,** in good to excellent yield ranging from 80-95%. Aliphatic alkynes 1-heptyne and 1-hexyne participated effortlessly in this multicomponent reaction and furnished product **4b, 4c** and **4k.** Not only aliphatic isothiocyanate like allyl isothiocyanate and cyclopropyl isothiocyanate but also substituted phenyl isothiocyanate and substituted benzoyl isothiocyanate engaged proficiently in this multicomponent reaction to furnish compounds **4a-o**.

The structure of thiazolidine-2-imine was unambiguously established by single crystal X-ray analysis of compound **4a**. These hydrothiolation reactions proceed, with a complete control over the stereochemistry. The exocyclic double bond formed was confirmed to be *Z*-isomer by single crystal X-ray analysis of **4a** (see supporting information).[10]

After successfully establishing the reaction conditions for the synthesis of thiazolidines **4**, we embarked on enantioselective variant of this multicomponent reaction. We had significant options with regards to ligand selection for carrying out this transformation in the enantioselective fashion. The mainstream of Cu-catalyzed asymmetric alkynylation reaction developed have utilized quinap[11], pinap[12], bis-imine[13] and

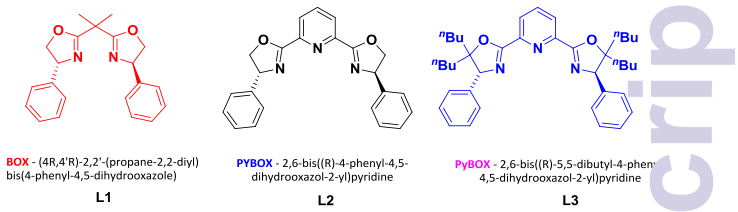
Table 2 Scope of Multicomponent Reaction Leading to the Synthesis of Thiazolidine-2-imine[a]



[a]All the reactions were performed with imine (0.50 mmol), acetylene (0.65 mmol) and isothiocyanate (0.55 mmol), 10 mol % CuOTf, solvent (3 mL) for 12 h at room temperature (30 °C).

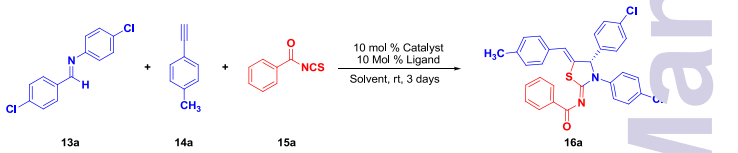
pybim[14] as ligands. Quest to find out new ligand with aim to increase the substrate scope of the asymmetric alkynylation reaction has led to discovery of pybox ligand.[15]

The problem, then, this multicomponent one-pot enantioselective synthesis of thiazolidine-2-imine presents is twofold: first acetylene has to undergo enantioselective addition on imine to form chiral propargylamine, and secondly the propargylthiourea intermediate formed by addition of propargylamine to isothiocyanate has to undergo regioselective (5 *exo dig vs* 6 *endo dig*) and chemoselective (hydrothiolation *vs* hydroamination) cyclization to form thiazolidine-2-imine. The difficulty of the task in our hand could be judged from the earlier reports that the relatively unhindered BINAP derived ligand was incapable to catalyze 5-*exo-dig* cyclization of propargylurea.[9] With the aim of finding the right catalyst and ligand combination for the multicomponent enantioselective synthesis of thiazolidine-2-imine, we used C_2 symmetric bisoxazoline ligand **L1, L2** and **L3** (Scheme 3). However, our initial attempts toward this end were severely jolted as we failed to achieve good enantioselectivity using ligand **L1** (Table 3 entries 1, 4 and 7).



Scheme 3 Chiral bis(oxazolinyl) ligands

Table 3 Effect of Conditions on the Enantioselectivity of the Multico mponent Reaction[a]



[a]entry	catalyst	ligand	Solvent	% yield[b]	*ee*[c] %
1	$CuPF_6$	L1	Toluene	80	5
2	$CuPF_6$	L2	Toluene	82	61
3	$CuPF_6$	L3	Toluene	82	70
4	$Cu(OTf)_2$	L1	Toluene	85	6
5	$Cu(OTf)_2$	L2	Toluene	86	65
6	$Cu(OTf)_2$	L3	Toluene	89	7
7	CuOTf	L1	Toluene	87	8
8	CuOTf	L2	Toluene	94	90
9	CuBr	L3	Toluene	71	6
10	CuBr	L2	Toluene	70	54
11	CuBr	L3	Toluene	71	58
12	CuOTf	L3	$CHCl_3$	76	65
13	CuOTf	L3	CH_3CN	60	60
14	CuOTf	L3	CH_2Cl_2	80	54
15	CuOTf	L3	EtOAc	71	42
16	CuOTf	L3	Toluene	90	9

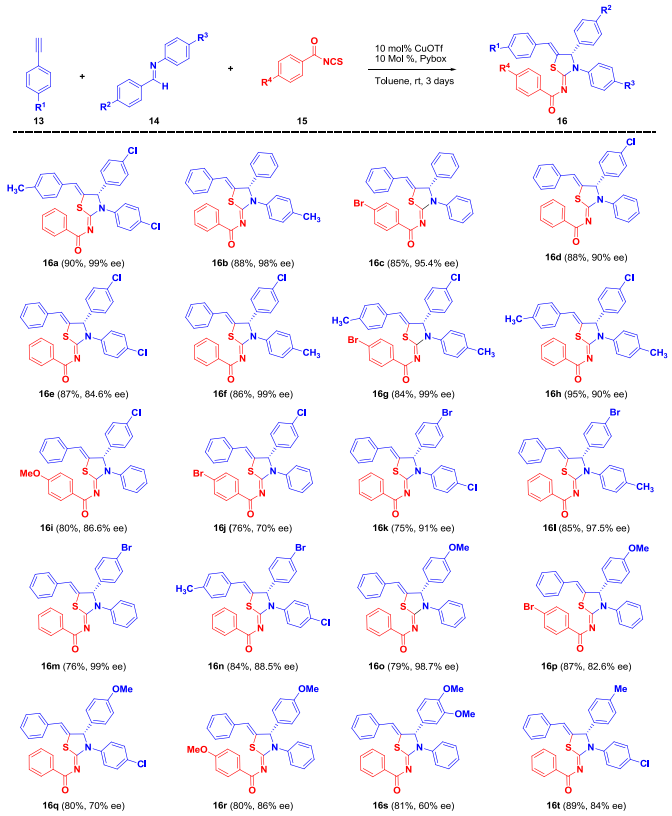
[a]All the reactions were performed with substituted imine (0.50 mmol), phenylacetylene (0.65 mmol) and benzoyl isothiocyanate (0.55 mmol), solvent (3 mL) for 3 days at 30 °C; [b]Isolated yield after colum chromatography; [c]Enantiomeric excess was determined by chiralcel OD- column using Isopropanol:hexane (1:19).

Singh *et.al* were able to get a high enantiomeric excess when they used i-Pr-pybox-diPh ligand having diphenyl group at th C-5 position of the oxazoline rings.[8]

Even though increase in enantioselectivity was observed whe ligand **L2** was employed in the reaction (Table 3 entries 2, 5, 8 an 10), the enantioselectivity could be improved up to *ee* 90% (Table entry 8). Lastly we turned our attention to ligand **L3**, which has been successfully used by Kang *et.al* for an asymmetric room temperature (30 °C) desymmeterization of symmetric 2,2-disubstituted 1,3-diols to install all-carbon quaterna y stereocenter.[16] Use of ligand **L3** in combination with differe counter ions and solvents was competent but not very selective (Table 3 entries 6 and 11-15). To our relief, high enantioselectivi y (99% *ee*) was achieved when Cu(I)OTf/**L3** was employed as a catalyst system, (Table 3 entry 16). Temperature studies indicate that the product was obtained in good yield with excelle

enantioselectivity when the reaction was conducted at 30 °C. Lowering of the catalyst loading to 5 mol % led to slower reaction rates. When the reaction was performed in 10 volume of toluene, decrease in chemo selectivity was detected and hydroamination product was formed along with hydrothiolation product.

Table 4 Scope of the Multicomponent Reaction using Cu(OTf) Toluene pybox Complex[a]



[a]Reaction conditions: All the reactions were performed with substituted imine (0.50 mmol), phenyl acetylene (0.65 mmol) and benzoyl isothiocyanate (0.55 mmol), 10 mol % CuOTf, 10 mol % pybox/L3, solvent (3 mL) for 3 days at 30 °C .

Having identified the optimum catalyst and reaction conditions, we set out to demonstrate the generality of our enantioselective protocol. The reaction was further extended to diverse imines, and the majority of them gave high enantioselectivity (Table 4). We obtained 99% *ee* when imine formed from 4- methoxybenzaldehyde (Table 4 entry **16o**) and 4-chlorobenzaldehyde was used, we obtained 99% enantiomeric excess (Table 4 entries **16a, 16f** and **16g**). Imine prepared from 3,4 dimethoxy benzaldehyde and aniline gave only 60% enantiomeric excess. (Table 4 entry **16s**) The yield obtained in this reaction was excellent in most of the cases. This three component reaction can be extended to *para* substituted phenylacetylene and *para* substituted benzoyl isothiocyanate. It is significant that the enantioselectivity was excellent in all types of substituted aromatic alkynes (Table 4 entries **16a** and **16c**) and isothiocyanate used (Table 4 entries **16b, 16g** and **16r**). The absolute configuration of the products was unambiguously assigned as "*S*" on the basis flack parameter[17] of the X-ray crystal structure of compound **16l.**

The stereochemistry of the exocyclic double bond was found to be *Z* (see supporting information).[10]

In summary, we have developed a system in which a copper catalysed both the alkynylation and the subsequent 5-*exo*-*dig* cyclization of the corresponding propargylthiourea to afford cyclic five-membered thiazolidine-2-imines. This cascade reaction forms a C-C, N-C and C-S bond in a one-pot. The importance of the chemistry described here lies in the established new synthetic method to prepare wide variety of thiazolidine-2-imine using mild reaction conditions. The chiral Cu(I)OTf and pybox/**L3** complex was established to be new and an efficient catalyst for the enantioselective three-component synthesis of thiazolidine-2-imines from imines, alkynes and isothiocyanates. The method is very simple, furnished a wide variety of thiazolidines in good to excellent yields (up to 95%) with excellent enantioselectivities (up to 99% *ee*).

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