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Review

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Progress in metal-catalysed trifluormethylation reactions using hypervalent iodine reagents

Ritu Mamgain,[a] Revati Nagarkar,[b] and Fateh V. Singh*[a]

[a]Chemistry Division, School of Advanced Sciences (SAS), Vellore Institute of Technology -Chennai, Vandalur-Kelambakkam Road, Chennai -600127, Tamil Nadu, India
[b]Chemistry Department, Modern College of Arts, Science and Commerce, Ganeshkhind, Pune, Maharashtra, 411016,India
Email: fatehveer.singh@vit.ac.in

Dedicated to Prof Thomas Wirth

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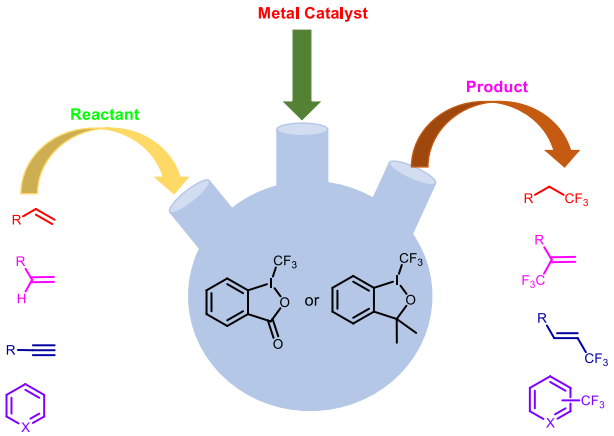
Abstract

The trifluoromethyl group is found in a variety of pharmaceuticals, agrochemicals, and functional organic compounds due to its ability to improve properties like electronegativity, hydrophobicity, metabolic stability, binding selectivity, and bioavailability. As a result, the development of innovative techniques for the incorporation of trifluoromethyl group has long been a research focus. Various metals such as Cu, Mg, Ni, Ag, Fe, and V were found to act as lewis acid in the synthesis of different trifluoromethylated compounds. In this review, the recent development of metal-catalyzed trifluoromethylation of C-C, C-N, C-O multiple/single bonds using hypervalent iodine reagent is described.



Keywords: Metal-catalyzed reaction, hypervalent reagents, trifluoromethylation, Tognireagent

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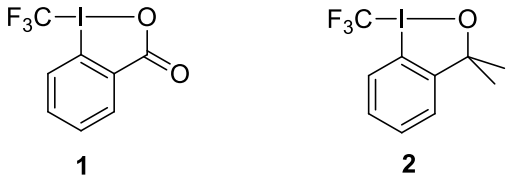
1. Introduction

Trifluoromethyl group is frequently found in pharmaceuticals, agrochemicals, and functional organic materials. The ability to improve properties like electronegativity, hydrophobicity, metabolic stability, binding selectivity, and bioavailability makes the trifluoromethyl (-CF_3) group a privileged moiety.[1-3] As a result, strategies for introducing a trifluoromethyl group into small molecules are critical, and much work has been expended in developing efficient methods for selective integration of the -CF_3 group into various skeletal structures.[4-13] Among the numerous methods for adding -CF_3 into the molecule, transition metal-mediated or -catalyzed trifluoromethylation has received the greatest interest since it allows the easy formation of both C–C, C–heteroatom, and C–CF_3 bonds in a single step.[14-17] Hypervalent iodine reagents are eco-friendly and extensively used as oxidants and electrophilic reagents in organic transformations.[18-26] The chemistry of hypervalent iodine reagents is now well explored and various book chapters and review articles have now appeared.[27-42] Other than oxidation the reagents under suitable conditions can also be used for ligand exchange, reductive elimination reaction, ligand coupling, radical type reactions, homolytic reactions, and single electron transfer reactions.[43] The following common reagents have been used as the source of trifluoromethyl group in the hypervalent iodine promoted reactions: Langlois reagent (CF_3SO_2Na)[44-51] Ruppert–Prakash reagent (CF_3SiMe_3)[52-57] Umemoto's reagent[58-62] and Togni reagent.[63-75] Among them, 1-(trifluoromethyl)-1,2-benziodoxol-3(1H)-one **1** and trifluoromethyl-1, 3-dihydro-3,3-dimethyl-1,2-benziodoxole **2** (figure 1), commonly known as Togni reagent proved to be powerful electrophilic trifluoromethylation agent for a variety of chemical reactions[76], owing to its stability, versatility, and commercial accessibility. Although Togni reagent can react directly with nucleophiles[77], an auxiliary medium, such as Bronsted acid[78,79] a transition metal complex acting as Lewis acid[80,81] or transition metal acting as reducing agent[82-86] is required to create the CF_3 radical.



1 **2**

Figure 1. Hypervalent iodine reagents.

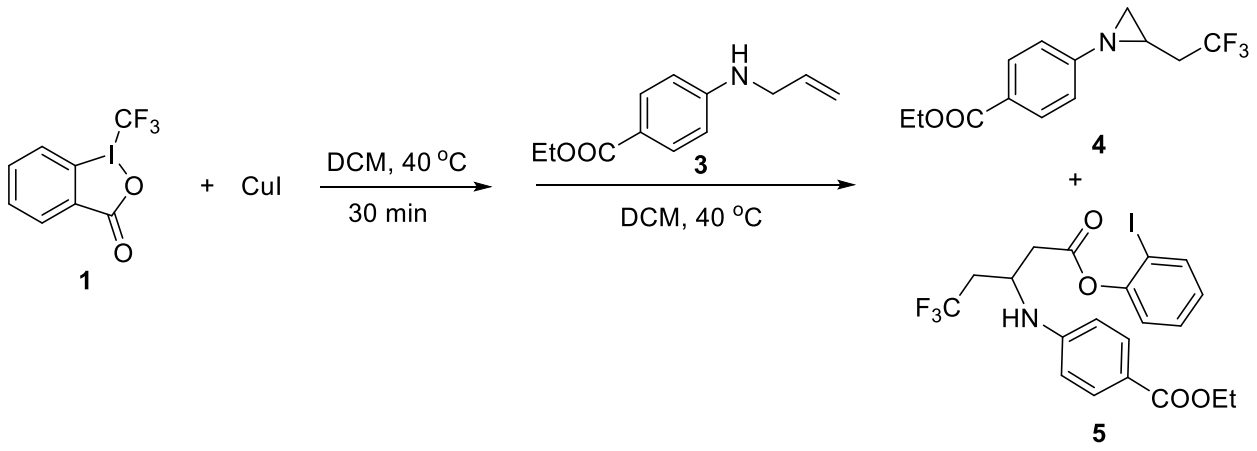
This review summarizes the literature data that includes the transfer of the trifluoromethyl group from the hypervalent reagents **1** and **2** to different substrates. The presentation of the material is arranged based on different metal catalysts or metal-ligand complexes used as catalysts. This review covers the literature published in or after 2015.

2. Metal-Catalyzed Trifluoromethylation

Trifluoromethylations, particularly those mediated or catalyzed by transition metals, easily provide a wide number of CF_3-containing molecules. The transition metals are well documented to act as the lewis acid and help in the synthesis of CF_3 substituted products. Wide arrays of reactants were compatible in this reaction ranging from simple alkanes, alkenes, and alkynes to aromatic compounds. Further, this section is classified based on the synthesis of trifluoromethyl substituted molecules using different metal catalysts in presence of hypervalent iodine reagents.

1.1. Copper-Catalyzed Trifluoromethylation

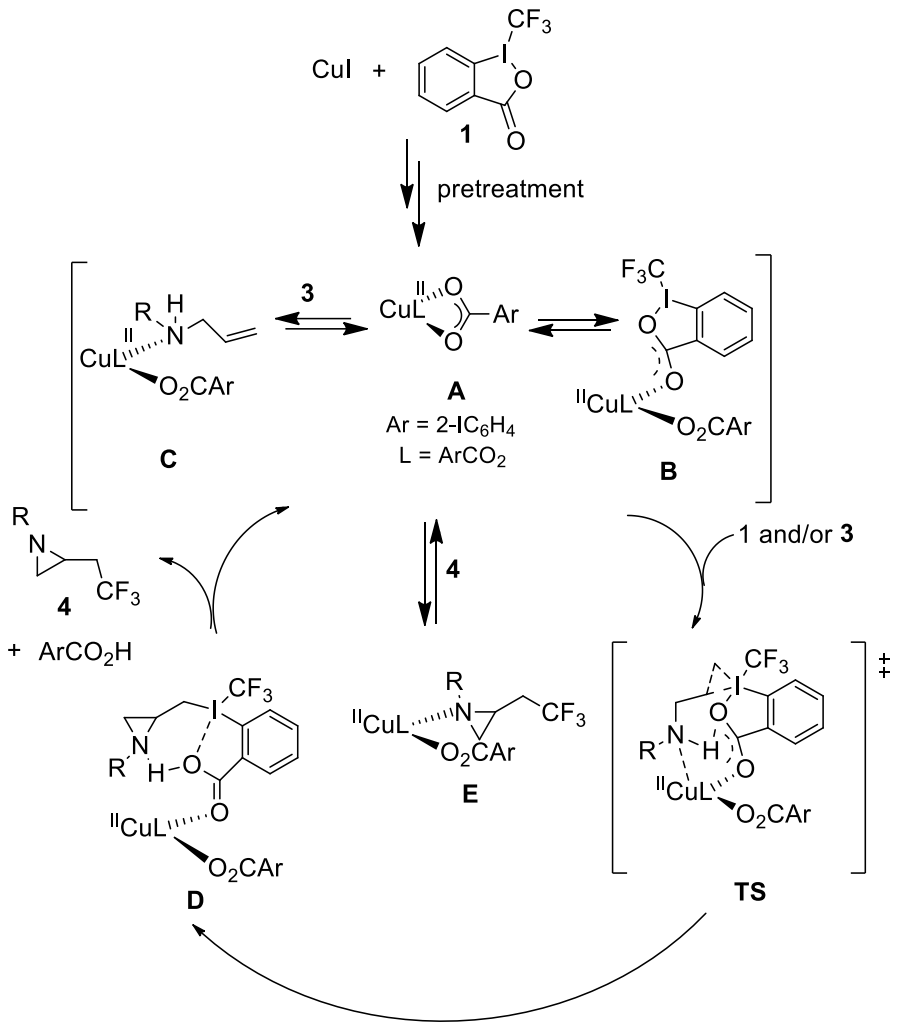
Many trifluoromethylated products are obtained in the trifluoromethylation reactions in presence of a copper catalyst. The trifluoromethylation reaction using hypervalent reagents **1** and **2** were predicted to have two mechanistic pathways. One of the proposed mechanisms involves the generation of trifluoromethyl radical as a key intermediate, which reacts with olefins or forms Cu−CF_3 species while the other proposed mechanism involves the use of copper as a lewis acid which activates the Togni reagent (**1** or **2**) by enhancing the electrophilicity of the hypervalent iodine. A later mechanism is based on the original mechanism proposed by Togni during the reaction of trifluoromethylation of alcohols in the presence of zinc salts. So, to explore the mechanism of copper catalyzed trifluoromethylation of olefins, Shintaro Kawamura and coworkers carried out a detailed mechanistic study.[87] Trifluoromethylation of less reactive allylamine bearing ethyl benzoate group **3** using CuI catalyst and Togni reagent **1** to give aziridine product **4** and **5** was chosen as a model reaction for this study (Scheme 1). The effect of pretreatment was investigated by mixing CuI and Togni reagent **1** in CH_2Cl_2 at 40 °C for 30 minutes before adding substrate **3** to the reaction mixture. It was observed that pretreatment not only increases the reaction rate but also improves the product selectivity of **4**. When Togni reagent and allyl amine in DCM were warmed to 40 °C, no product formation was observed in absence of Cu catalyst. An initial kinetic study proved that the rate of reaction depends on the concentration of Togni reagent **1**, CuI, and allyl amine and follows the first-order relationship.



Scheme 1. Cu-catalysed trifluoromethylation of ethyl 4-(allylamino)benzoate **3** using hypervalent iodine reagent **1** to aziridines **4.**

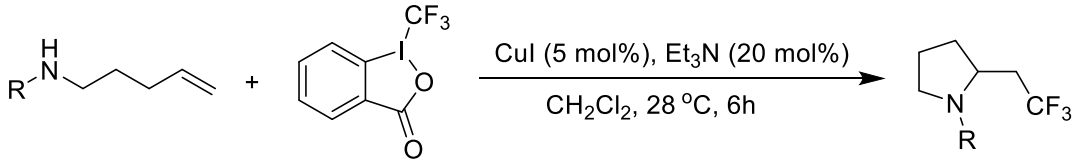
To identify the reactive copper species, Togni reagent **1** and CuI were reacted to obtain green crystals. Further, the crystal structure identified by X-ray showed that the complex was Cu (II) dimer bridged by four 2-iodobenzoates with two solvent molecules as additional ligands without a trifluoromethyl group. When this complex was further reacted with allylamine, desired aziridine product was observed in 66% yield. This proved that Cu(II), 2-iodobenzoate species were catalyzing the reaction. Further presence of the trifluoromethyl group in the reaction mixture was confirmed by ^{19}F NMR spectroscopy. On reacting the copper dimer formed earlier and CuI with Togni reagent **1**, it was observed that the chemical shift of Togni reagent in ^{19}F NMR was shifted to a lower magnetic field after the addition of CuI and the two peaks arriving from both the mixtures appeared at the same value. Further ESI-MS spectra of the two mixtures were almost identical, which indicated the presence of the same intermediates.

All the above results suggest that the oxidation of CuI with hypervalent iodine reagent **1** gave Cu(II) species that act as a Lewis acid as shown in scheme 2 and was confirmed by ESI-MS analysis. The electrophilicity of the O-I bond of Togni reagent **1** is enhanced by the formation of intermediate **B**, which is in equilibrium with intermediates **A** and **C** in presence of allyl amine **3**. Intermediate **B** or **C** further reacts with allyl amine **3** to give a transition state (**TS**) which is postulated based on kinetic experiments. The transition state breaks into intermediate **D**, which after ligand coupling gives back intermediate **A** via formation of the desired product.



Scheme 2. Catalytic cycle for Cu-catalyzed trifluoromethylation reaction.

Further applications of this reaction in the synthesis of trifluoromethylated pyrrolidines **7** were studied. Substrate scope study revealed that reaction works well with various substituents on the phenyl ring of anilines as well as substituted double bonds **6** with satisfactory yields (Scheme 3).



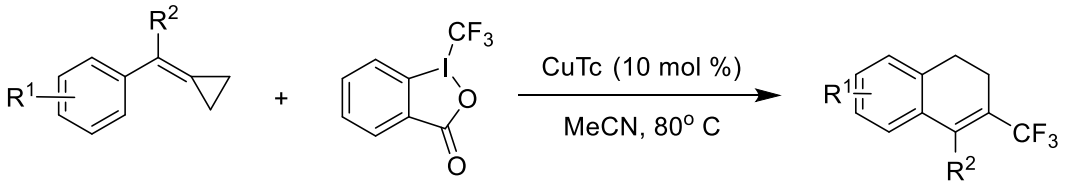
6 **1**

R = 4-OMeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$,4-IC$_6$H$_4$, Ts, Bn, 2-Me, 4-OMeC$_6$H$_3$, 1-Naph, Cy

,

Scheme 3. Cu-catalzed trifluoromethylation of olefin **6** using Togni reagent **1** to trifluoromethylated pyrrolidines **7.**

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules and are found to be important building blocks in organic synthesis. Zi-Zhong Zhu[88] and co-authors have explored a novel synthetic protocol for Cu(I)-catalyzed intramolecular trifluoromethylation of Methylenecyclopropanes (MCPs) **8** followed by ring expansion to give CF_3-substituted dihydronaphthalenes **9**. After screening different Cu catalysts, CuTc (thiophene-2-carboxylic acid- Cu) was found to be an effective catalyst. On the optimization of reaction, it was observed that reacting methylenecyclopropanes **8**, with 2 equivalents of Hypervalent iodine reagent **1** dissolved in acetonitrile in presence of 10 mol% of CuTc at 80° C gave product **9** in good yield. (Scheme 4). The procedure was well tolerated when evaluated for the various substituted MCPs. The product was obtained in moderate to excellent yield for various electron withdrawing and donating groups.



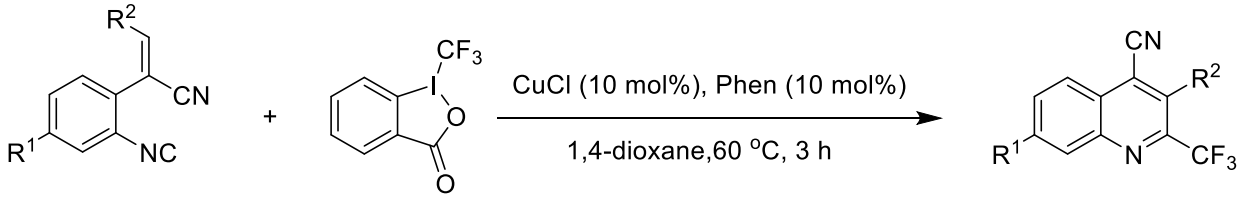
8 **1** **9: 50-83%**

R^1 = *o*-CH_2NHTs; o-NHTs; o-NO_2; *o*-CN; *m*-OBn; *m*-NHTs; *m*-NO_2; *p*-CN; *p*-Cl, *o* -OMe, *m* -OMe; *o*-OMe,*m* -Br; *o* -Br, *p* -Me; *o*-Br, *m,p*-OMe, R^2 = Ph, H

Scheme 4. Cu-catalyzed intramolecular trifluoromethylation of methylenecyclopropanes **8** with trifluoromethylating reagent **1** to CF_3-substituted dihydronaphthalenes **9**.

The presence of electron withdrawing substituents like –NO_2 or –CN at aromatic ring decreases the yield of reaction while electron donating groups like -NHTs, -OR increase the yield of the product. The synthetic utility of the product was demonstrated by its further transformations into useful trifluoromethylated compounds under mild conditions. The mechanistic studies showed that the reaction is catalyzed by CF_3 radical, generated with the help of Cu catalyst. The radical reaction was confirmed by using a radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy). On adding TEMPO the yield of the product decreased drastically to 28% as the CF_3 radical gets captured by TEMPO to give the corresponding TEMPO adduct in 22%. On the other hand, in presence of BHT (butylated hydroxytoluene) no product was obtained suggesting that the reaction may be procced via radical formation.

Shukuan Mao and coworkers[89] in 2020 discussed the 6-endo-trig radical cyclization of o-alkenyl aromatic isocyanides for the efficient one-pot synthesis of quinolines in presence of a copper catalyst and suitable ligands. To synthesize 4-cyano-2-trifluoromethyl/difluoromethyl containing quinolines **11**, a mixture of (E)-2-(2-isocyanophenyl)-3- phenylacrylonitrile **10** and Togni reagent **1** dissolved in 1,4 –dioxane was treated with CuCl (10 mol%) and Phen (10 mol%) at 60 °C for 3 h (Scheme 5). The CuCl gave a good yield in comparison to the other Cu catalysts viz. CuI, $Cu(MeCN)_4PF_6$, CuBr, and $Cu(OAc)_2$. Various solvents like DCM, $CHCl_3$, 1,4 –dioxane, DCE, DMF, DMSO, THF, MeOH, and HFIP were explored among which 1,4 dioxane gave the best yield. In comparison to Phen other ligands such as Dtbpy, Bipy and DMEDA were not able to promote the reaction.



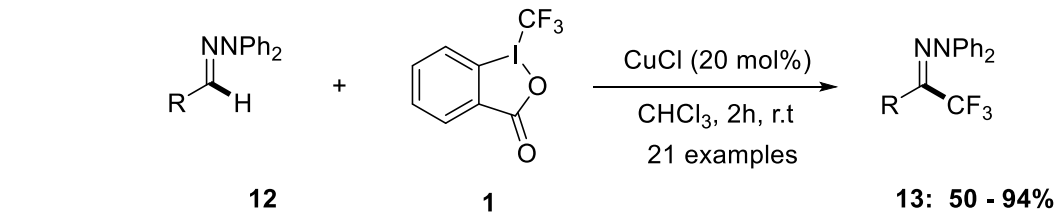
10 **1** **11: 60-84%**

R^1 = H, F; R^2 = C_6H_5, *p*-MeC_6H_5, *p*-BuC_6H_5, *p*-FC_6H_5, *p*-ClC_6H_5, *p*-BrC_6H_5, *p*-CNC_6H_5, *p*-CFC_6H_5, *m*-FC_6H_5, *m*-ClC_6H_5, *m*-CNC_6H_5, *o*-MeC_6H_5, *o*-BrC_6H_5, *m,p*-MeC_6H_3, o,p-ClC_6H_3.

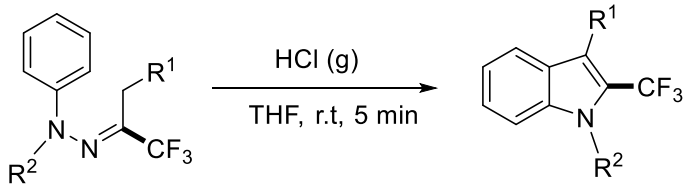
Scheme 5. Cu-catalysed cyclization of o-alkenyl aromatic isocyanides **10** to 4-cyano-2-trifluoromethyl quinolones **11** using Togni reagent **1** as the CF_3 source.

On studying the substrate scope, it was observed that a variety of isocyanides were well tolerated resulting in moderate to high yield of the products. Substrates bearing both electron-donating and electron-withdrawing groups at the para-positions of the phenyl ring were also endured to give moderate to excellent yields. For further optimization, the reaction was performed with visible-light photoredox catalysis or through a Bu_4NI radical initiator promotion strategy, which gave comparatively lower yields. Replacement of Togni reagent **1** with stable and easily accessible difluoromethyltriphenylphosphonium bromide failed to incorporate CF_2H in the reaction under the same conditions. However further optimization of the 6-endo-trig radical cyclization reaction; another product 4-cyano-2-difluoromethyl quinoline was obtained in 70% yield by visible-light photoredox catalysis. It was found that o-alkenyl aromatic isocyanides bearing different electron-withdrawing and electron-donating groups at the ortho-, meta-, and para-position of phenyl ring were fully tolerated with moderate to high yield of the 4-cyano-2-difluoromethyl quinoline. The mechanism of the reaction was determined using radical scavenger TEMPO which indicated the generation of CF_3 radical formed by a combination of Togni reagent **1** and Cu(I) catalyst. This radical chemoselectively attacked the isonitrile, giving a corresponding imidoyl radical intermediate which further followed the 6-endo or 5-exo mechanism and gave substituted quinolines.

Alexis Prieto et. al in 2015 developed a simple procedure for the trifluoromethylation of N, N substituted hydrazones in presence of hypervalent iodine and a copper catalyst.[90] The N, N-diphenylamine with terminal hydrazone amino group **12** when stirred in presence of CuCl (20 mol%) as a catalyst and hypervalent iodine reagent **1** as a source of trifluoromethyl group at 25 °C for 2 h afforded product **13** in moderate to excellent yield (Scheme 6). Various substituents and functional groups, including thiomethyl, benzyloxy, halide, and free hydroxyls were well tolerated. Trifluoromethylated N-aryl hydrazones **14** prepared by the above method are shown to be an important starting material for the synthesis of trifluoromethyl ketones and 2-trifluoromethylindole derivatives **15**. When the reaction was carried out in presence of HCl (g) in THF solvent, the formation of indole product was observed in 5 min. Different substituents like phenyl, benzyl, and thiols are well tolerated resulting in substituted indoles **15** in 91% yield (Scheme 6).



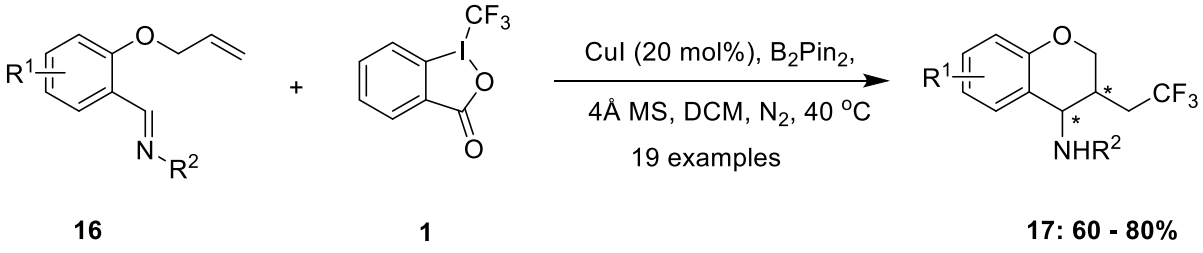
R = H, CH_3, $(CH_2)_3CH_3$, $(CH_2)_3Cl$, $(CH_2)_2SCH_3$, $(CH_2)_2OBn$, $CH_2C_6H_5$, $(CH_2)_2C_6H_4Br$, $CH_2(CH_3)_2$, $CH(CH_3)_3$,COOEt



R^1 = CH_2SCH_3, $(CH_2)_2Cl$, $CH_2C_6H_4Br$, $CH_2C_6H_5$; R^2 = Ph,

Scheme 6. Cu-catalyzed trifluoromethylation of N, N-disubstituted hydrazones **12** using hypervalent iodine reagent **1** to trifluoromethylated hydrazine **13** a starting material for 2-trifluoromethylindole derivatives **15.**

Qin Ye and group synthesized biologically important 3,4-Dihydro-2H-1-benzopyrans **17** (chromans) using ene-imine **16** and hypervalent iodine reagent **1**.[91] For the synthesis of desired product, the optimized conditions required stirring of ene-imine **16** with 1.6 equiv. of Togni reagent **1**, in presence of Bis(pinacolato)diboron (B_2Pin_2), 4Å molecular sieves, and 20 mol% of CuI in DCM at 40 °C for 9h (Scheme 7). Molecular sieves were added to avoid decomposition of ene-imine **16**. Under optimized conditions, the yield obtained of compound **17** (R_1, R_2 = H) was 81% with a ratio of anti: syn 1.8:1, which was confirmed by NOE experiment.

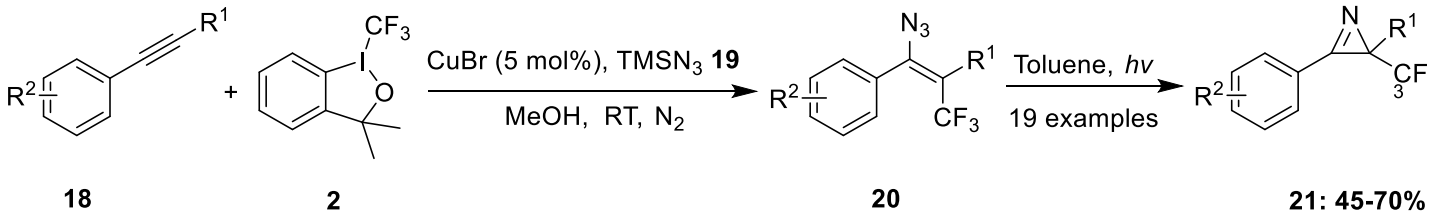


R^1 = H, R^2 = *p*-$CH_3C_6H_5$, *o*-$CH_3C_6H_5$, *m*-$CH_3C_6H_5$, *p*-$OMeC_6H_5$, *p*-ClC_6H_5, *p*-BrC_6H_5, *p*-FC_6H_5, *m*-$(CH_3)_2C_6H_4$
R2 = H, R1 = C_6H_4, *o*-$CH_3C_6H_3$, *m*-$CH_3C_6H_3$, *p*-$CH_3C_6H_3$, *p*-$OMeC_6H_3$, *p*-ClC_6H_3, *p*-Br-C_6H_3, $NO_2C_6H_3$, *p*-$COOMeC_6H_3$,

Scheme 7. Cu-catalysed intramolecular carbotrifluoromethylation of ene-imines **16** in presence of trifluoromethylating reagent **1** and B_2Pin_2 to 3,4-dihydro-2H-1-benzopyrans **17.**

Further substrate scope was studied for the ene-imines with electron donating substituent at ortho and meta position to ether gave the expected products in good yields, but ene-imines with electron withdrawing or electron donating substituent at the para-position to ether gave the corresponding products in moderate to low yields. Further, the ene-imine **16** with a butenyl group was allowed to undergo intramolecular carbotrifluoromethylation to give 43% yield of the seven-membered ring product.

The use of radical scavenger 2,2,6,6-tetramethyl-1- piperidinyloxy (TEMPO), 2,6-di-tertbutyl-4-methyl phenol (BHT, 2.0 equiv) in reaction reduces the yield drastically which proves radical mechanism. CF_3 radical is generated through the reaction between Cu(I) and Togni reagent **1** which further attacks on less substituted carbon of double bond to give radical intermediate. The intramolecular cyclization of the radical intermediate afforded nitrogen radical. This radical is captured by B_2Pin_2 to give an intermediate Borinamide which readily was hydrolyzed to give the product.



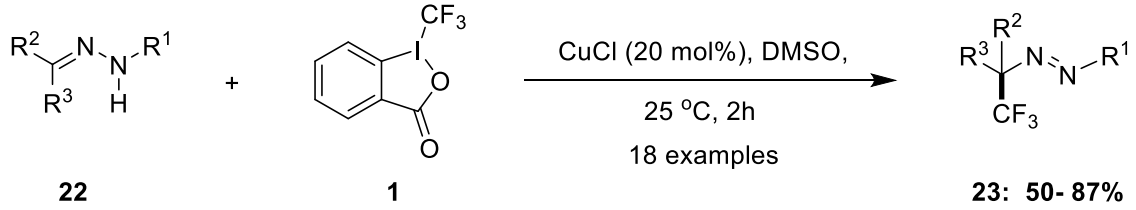
R^1 = H, Me,TMS, Ph, CH_2OH; R^2 = H,
p-Cl, *p*-F, *p*-Br, *p*-CH_3, *p*-OMe, *p*-NO_2

Scheme 8. Cu-catalyzed trifluoromethylation of alkyne **18** using Togni reagent **2** as CF_3 radical generator and $TMSN_3$ to triflurometyl substituted azirines **21**.

Aziridines and azirines, the smallest nitrogen-containing heterocycles, have been identified as significant pharmaceutical and insecticide precursors. Fie Wang and coworkers[92] proposed a novel method for the synthesis of CF_3 containing azirines using the copper catalyst and hypervalent iodine reagent which were further easily converted into the corresponding CF_3 substituted aziridines. The first step includes synthesis of CF_3 substituted alkenes **20** from alkyne **18** using 5 mol % Cu-catalyst, $TMSN_3$ **19** in methanol at R.T. Further on irradiation by high-pressure mercury lamp (100 W) and in presence of toluene photo-catalyzed rearrangement occurred to afford the final product azirines **21** in excellent yield (Scheme 8). Amongst the different metal catalysts screened, such as $[Cu(CH_3CN)_4]OTf$, $Cu(OAc)_2$, CuBr, CuI; CuBr was found to be the most effective catalyst. Metal catalysts other than copper were found to be inert for the reaction. Hypervalent iodine reagent **2** in comparison to other reagents gave a good yield in presence of methanol as a solvent. Both terminal and internal alkynes were compatible with the mild reaction conditions, resulting in moderate to excellent yields of CF_3-containing azirines. Arylacetylenes having various electron-donating and electron-withdrawing substituents like halogen, ester, nitro, and amide groups on the aromatic ring were compatible with good yields. Substrates with heteroaryl groups, such as quinolinyl and pyridyl also proceeded smoothly to give satisfactory yields. It was observed that when two alkynes are present in the molecule the reaction occurred only at aryl conjugated alkyne with an excellent yield of the delivered product. Azirines containing CF_3 **21** when coupled with different nucleophiles resulted in the corresponding substituted aziridines in excellent yield along with excellent diastereoselectivity. Further cyanation of aziridines using TMSCN was also carried out.

Diazenes are key organic reagents that are used in a broad range of reactions, including cycloadditions[93-95] and radical reactions.[96-99] Alexis Prieto and group[100] discussed the Trifluoromethylation of

ketone derived hydrazone. Pyruvate N-methylhydrazone **22** was picked as starting material for the model trifluoromethylation reaction. The maximum yield of product **23** was obtained in presence of CuCl catalyst in solvent DMSO (Scheme 9) compared to other Cu catalysts and polar solvents. Next, the scope of the reaction was studied by changing R^1 and R^2 substituents as phenyl, substituted phenyl, or alkyl groups which gave good yields of the corresponding arylazenes. It was observed that reaction works well with sterically crowded ketone derivatives with good yield. Unfortunately, with electron-donating substituents on acetophenone-derived hydrazones, the reaction did not work well. Furthermore, the synthetic usefulness of the trifluoromethylation process was demonstrated by the synthesis of a CF_3 -hydrazine derivative by reduction of diazene with H_2 in the presence of Pd/C within 3 h.

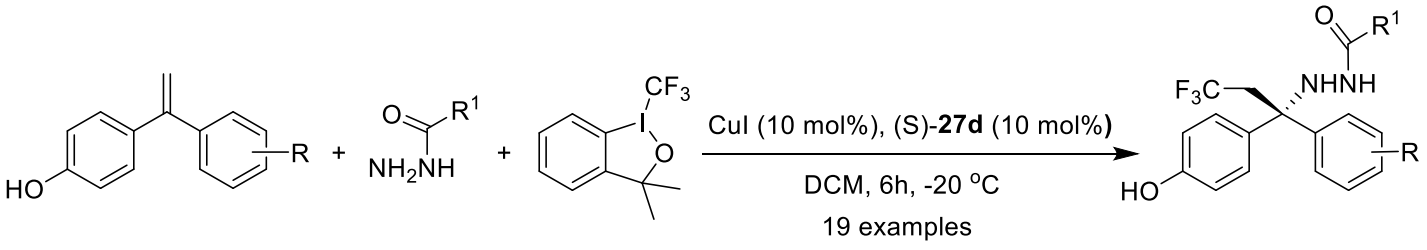


22 **1** **23: 50- 87%**

R^1 = CH_3, $C(CH_3)_2$, C_6H_5, *p*-$OMeC_6H_4$, R^2 = CH_3, $CH_2CH(CH_3)_2$,
R^3 = CH_3, COOEt, $COOCH_2C_6H_5$, *p*-$NO_2C_6H_4$, *p*-CNC_6H_5, *p*-BrC_6H_5, *p*-ClC_6H_5, *p*-$OMeC_6H_5$, *m*-$NO_2C_6H_5$, *m*-CNC_6H_4

Scheme 9. Cu-catalysed Trifluoromethylation of pyruvate N-methylhydrazone **22** in presence of hypervalent iodine reagent **1** to quaternary α-trifluoromethyl diazenes **23**.

Zhe Wang and group for the first time demonstrated catalytic enantioselective radical-involved intermolecular aminotrifluoromethylation of alkenes.[101] The reaction involves efficient asymmetric intermolecular radical aminotrifluoromethylation of *p*-hydroxy 1,1-diarylalkenes **24** with nitrogen nucleophiles $BzNHNH_2$ **25** in presence of hypervalent iodine reagent **2** and Cu(I)/chiral phosphoric acid (CPA) 10 mol% catalyst to get corresponding product **26** in good yield with high enantioselectivity (Scheme 10).



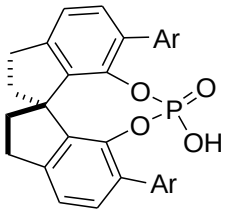
24 **25** **2** **26: 70 - 95%, *ee:* < 86%**

R = *p*-CH_3, *p*-Ph, *p*-^{t}Bu, *p*-NO_2, *p*-CN, *p*-CF_3, *p*-F, *p*-Cl, *p*-Br, *p*-I

R^1 = C_6H_5, *p*-$CH_3C_6H_4CO$, *p*-$OMeC_6H_4$,CO, *p*-^{t}BuC_6H_4CO, *m*-FC_6H_4CO, *o*-FC_6H_4CO, $CH_2C_6H_4CO$

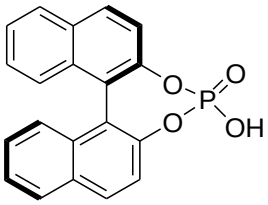
Scheme 10. Enantioselective intermolecular radical aminotrifluoromethylation of 1,1-diarylalkenes **24** with hydrazines and hypervalent iodine reagent **2** in presence of Cu(I)-CPA dual catalyst.

Different copper salt with diverse SPINOL and BINOL derived CPA (figure 2) were screened for the reaction and it was observed that the combination of CuI 10 mol% and **27d** 10 mol% was the best dual catalyst. In absence of CPA traces of the product were obtained making it clear that a dual catalyst is necessary as a single-electron catalyst to activate the hypervalent iodine reagent to give CF_3 radical. On lowering the temperature to -20 °C enantioselectivity of the product increased although no change in chemical yield was observed. Further scope for substituents on the alkenes was studied and it was observed that the 1,1-diarylethylenes having electron-withdrawing groups on the phenyl ring, gave better enantioselectivity than those having electron-donating groups and R group at the meta position. Furthermore, a range of substituted hydrazines was well tolerated to furnish the corresponding products in excellent yields and enantioselectivity. The utility of the product was proved by converting it to synthetically pivotal intermediates.



27

(S)-**27a) :** Ar = 4-Ph-C_6H_4
(S)-**27b) :** Ar = 2-naphthy-Ph
(S)-**27c) :** Ar = 1-pyrenyl
(S)-**27d) :** Ar = 4-tBu-C_6H_4-C_6H_4

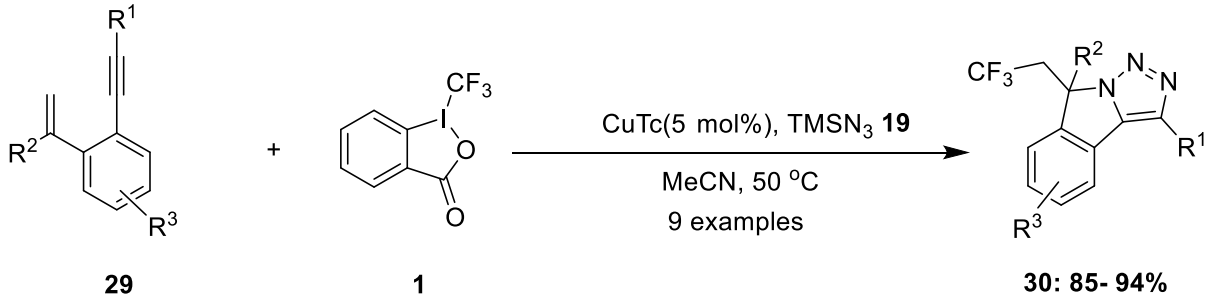


28

(R)-**28a):** Ar = 4-Ph-C_6H_4
(R)-**28b):** Ar = 1-pyrenyl

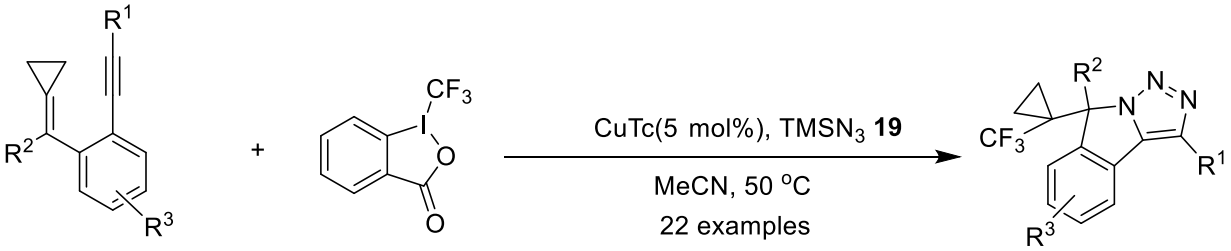
Figure 2. Chiral phosphoric Acids along with Cu-catalyst screened for aminotrifluoromethylation of 1,1-diarylalkenes **24** with hydrazines.

Liu-Zhu and coworkers[102] reported a copper-catalyzed tandem cyclization of 1,5-enynes in the presence of hypervalent iodine reagent and nucleophile trimethylsilyl azide to give triazole fused isoindolines. The reaction proceeds through consecutive trifluoromethylazidation or diazidation and intramolecular click reaction. Different reaction conditions were screened to identify the optimal reaction conditions which include reacting 1 equiv. of substrate **29** with 1.5 equiv of hypervalent iodine reagent **1** in presence of 0.05 equiv CuTc catalyst with 2.0 equiv of $TMSN_3$ **19** under an inert atmosphere using acetonitrile as the solvent at 50 °C for 6 h to get an excellent yield of the corresponding triazole fused isoindolines **30** (Scheme 11). The reaction is reported to be well tolerated towards different substrates on alkene as well as alkyne phenyl group resulting in good to excellent yields of the products. Internal alkenes were also found to be compatible with the hypervalent iodine reagent and reaction conditions giving a good chemical yield with 1:0.6 diastereoselectivity. Further identification of the trifluoromethylcyclopropyl group as an important functional group with a wide scope in synthesis; encouraged authors to widen the scope of the reaction. The reaction worked well with a variety of substituents on substrate **31** with no obvious impact of the electronic effect on the yield of corresponding products **32**. In most of the cases, the yield obtained was good to excellent except R^2 was not substituted resulting in a 50% yield of the corresponding product.



29 **1** **30: 85- 94%**

R^1 = C_6H_5; R^2 = CH_3, *p*-^{t}BuC_6H_4, C_6H_5, 2-MeC_6H_4, 4-Cl C_6H_4; R^3 = C_6H_5, 2-NO_2, 2-Cl, H

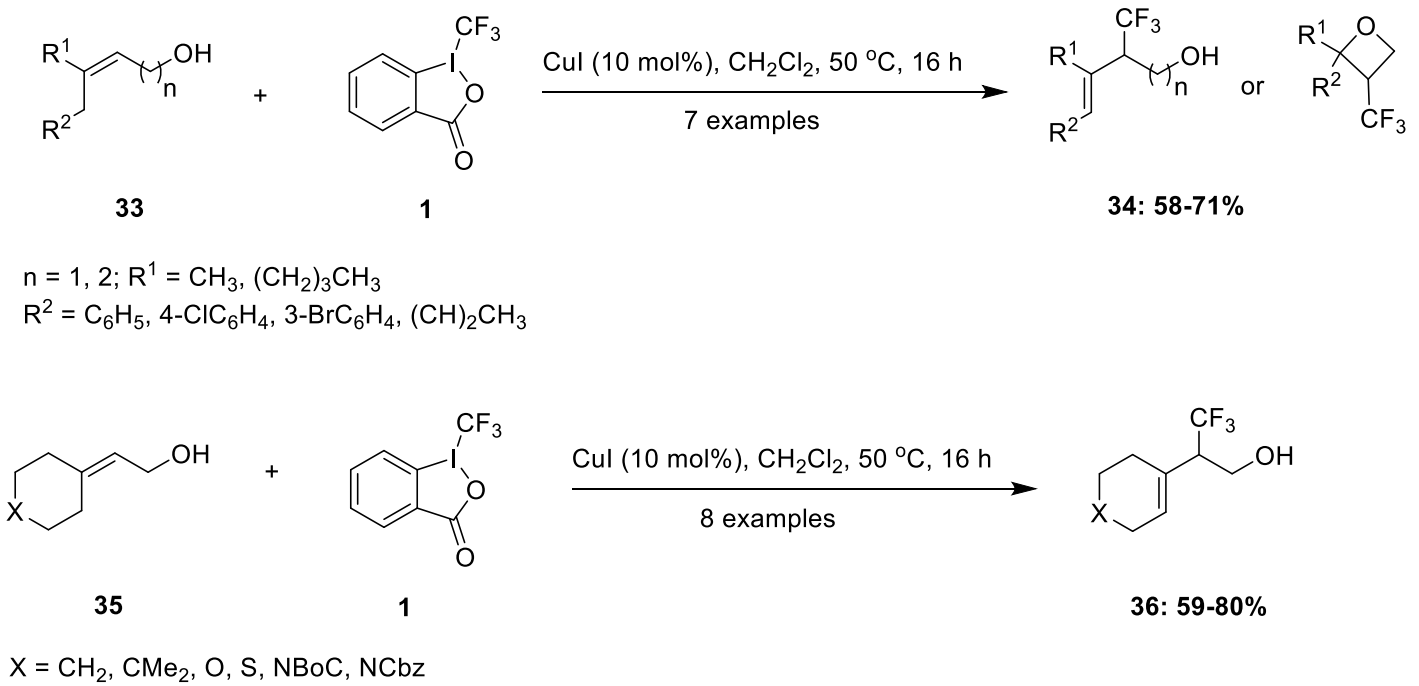


31 **1** **32: 70- 89%**

R^1 =H, $(CH_2)_3CH_3$, C_6H_5, Cyclopropane;
R^2 = C_6H_5, 4-MeC_6H_4, 4-MeOC_6H_4, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 3-MeC_6H_4; R^3 = H, C_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 3-FC_6H_4, 2-MeC_6H_4

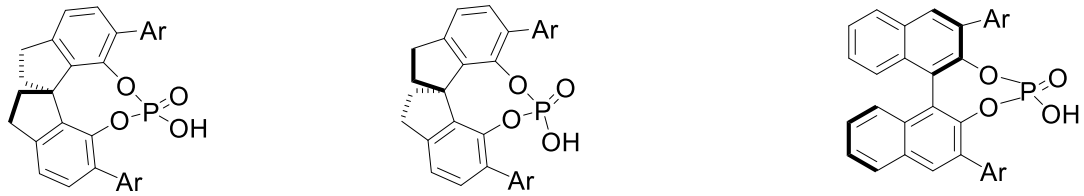
Scheme 11. Cu-catalysed cascade cyclization of 1,5 enynes **29 and 31** with hypervalent iodine reagent **1** to triazole fused trifluromethyl substituted isoindolines **30** and **32.**

Lei Jian et al developed copper catalyzed trifluoromethylation of trisubstituted allylic and homoallylic alcohols using hypervalent iodine reagent under mild conditions.[103] The optimized reaction condition for allylic and homoallylic alcohol **33, 35** are hypervalent iodine reagent **1** in presence of CuI as a catalyst, DCM as solvent at 50 °C to yield products **34** and **36** (Scheme 12). The yield of the reaction drops on performing the reaction at room temperature. On using other solvents like methanol, DMF, DMSO, and DCE the yield decreases drastically. Other copper catalysts like CuCl and CuTc were not as effective as CuI. The reaction endured well for different styrene substrates and trisubstituted aliphatic allylic alcohols. On using substituted 1,3-benzodioxole an electron rich aryl group as a substrate for the reaction the major product obtained was trifluoro substituted oxetane ring (yield 25%) along with the normal product (12%). The oxetane ring is the result of an intramolecular nucleophilic attack of an alcoholic oxygen atom on the potential benzylic radical or cation intermediate. Authors have also pioneered the synthesis of acyclic trialkyl substituted alkenes. On using trisubstituted alkene with no free hydroxyl group no reaction occurred, at the same time on protecting the hydroxy group with methyl the yield dropped drastically indicating the importance of the hydroxy group in the reaction. The alcohol and alkene functional groups serve as important building blocks.



Scheme 12. Cu-catalyzed trifluoromethylation of trisubstituted allylic and homoallylic alcohols **33, 35** with hypervalent iodine reagent **1.**

To develop the asymmetric radical aminotrifluoromethylation of alkenes, a dual-catalytic system consisting of a copper(I) source and a chiral phosphoric acid (CPA) **37** (figure 3) was used as an efficient catalytic system by Jin-Shun Lin et al.[104] The reaction of different N-protecting groups of alkenyl amines **38** with hypervalent iodine reagent **2** was carried out in presence of CuI (10 mol %) and CPA(S)-A1 (15 mol %) **37** to give CF_3-containing chiral pyrrolidines **39** with an α-tertiary stereocenter (Scheme 13).



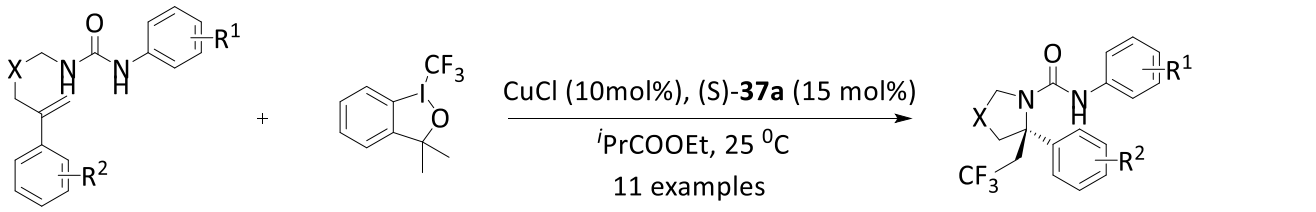
(S)-37a: Ar= 4-Ph-C_6H_4
(S)-37b: Ar= 4-Cl-C_6H_4
(S)-37c: Ar= 1-Naphthyl

(R)-37d: Ar=9-Phenanthryl
(R)-37e: Ar= 2-Naphthyl
(R)-37f: Ar=Ph

(R)-37g: Ar=4-NO_2-C_6H_4
(R)-37h: Ar= 2-Naphthyl

Figure 3. Chiral phosphoric acid (CPA) for screening of reaction.

Evaluation of different protecting groups of amines like amide, carbamate, or thiourea-protected amines and tosyl resulted in poor or no yields while the use of urea substrate resulted in improvement of yield and enantioselectivity in presence of EtOAc as a solvent. Further evaluation of BINOL and SPINOL based CPAs showed that selectivity of the reaction was based on substituents at 3,3' positions of the backbone and amongst them (**37a**) 4-Ph-C_6H_4 was found to be effective. CuCl (10 mol %) as a catalyst and ethyl isobutyrate as a solvent were found to be effective.



38 **2** **39: Yield 64-98%, ee: < 97%**

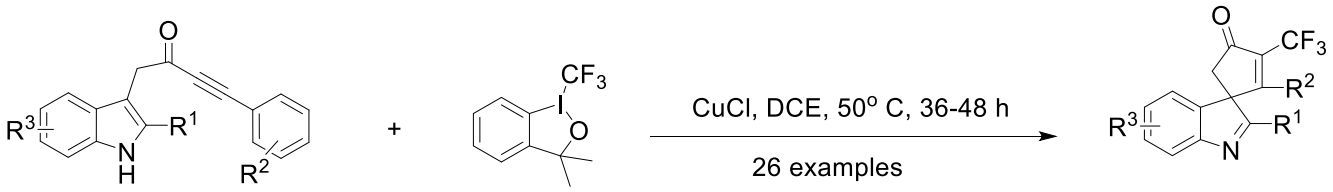
X = $C(CH_3)_2$, C_3H_4, C_4H_6, C_5H_8, C_6H_{10}, $C(COOEt)_2$, $C(COO^tBu)$
R^1 = 3,5-(CF_3); 4-CF_3; 3-CF_3; 4-F; 3-Cl; 4-Br; 3-Br; 3-Me; 3-OMe; 2-Br; 2-CF_3 ; R^2 = H, 3-OMe, 3-Me, 3-Ph, 3-F

Scheme 13. Asymmetric radical aminotrifluoromethylation of alkenes **38** using Cu(I)-CPA dual catalyst and Togni reagent **2** to CF_3 containing chiral pyrrolidines **39.**

After substrate scope study, it was found that reaction is well endured with electronic donating as well as electronic withdrawing substituents with high enantioselectivity. The position and electronic nature of the R^1 group attached to the phenyl ring of urea substrate showed negligible effect on yield as well as enantioselectivity except for the sterically crowded substituent at the ortho position.

The spiroindolenines are very much valuable and challenging molecules in organic synthesis. The regiospecific construction of trifluoromethylated spiro[cyclopentane-1,3'-indole] scaffolds containing quaternary spirocyclic carbon and tetrasubstituted alkenes **41** using indolyl ynones **40** with the Togni reagent **2** in presence of Cu catalyst is discussed in scheme 14.[105] For the optimization of reaction conditions, the substrate **40** (R^1=H) was reacted with Togni reagent **1** using CuI as a catalyst under argon atmosphere in DCM, but the yield of the reaction was very low. Gratifyingly when C-2 substituted substrate **40** (R^1 = CF_3) was used instead of R^1 = H and Togni reagent **1** was replaced by Togni reagent **2** in presence of CuCl and DCE the reaction yield was improved to 80%. With the optimization conditions in hand, next, the substrate scope was investigated using various indolyl ynones. As reported earlier, the use of 2-Ph indolylynone resulted in 88% yield and substitution of a 2-Ph group with halides or methyl resulted in moderate to good yield. The effect of the substituents on the phenyl ynones (Ar/R^2) like methoxy, chloro, bromo, n-butyl, or t-butyl showed that electron donating substituents improved the yield while electron withdrawing substituents decreased the efficiency. Next, the substrates with electron donating as well as withdrawing substituents at C-4 or C-7 substituents were well tolerated.

To explore the synthetic versatility of spiroindolenines, further organic transformations were carried out on 2-iodo substituents of **41.** The iodo functional group was converted into 2-mercaptoethanol (90% yield), ethynylbenzene (85% yield), CF_3-containing spirocyclicoxindole (99% yield, conversion of -I to -CO) successfully. Further, the reaction mechanism was determined using radical scavenger TEMPO under controlled conditions, and it was concluded that the reaction follows a radical pathway. The two mechanistic pathways were explored which involve regioselective attack of CF_3 radical at α-position to form a $C(sp^2)–CF_3$ bond.

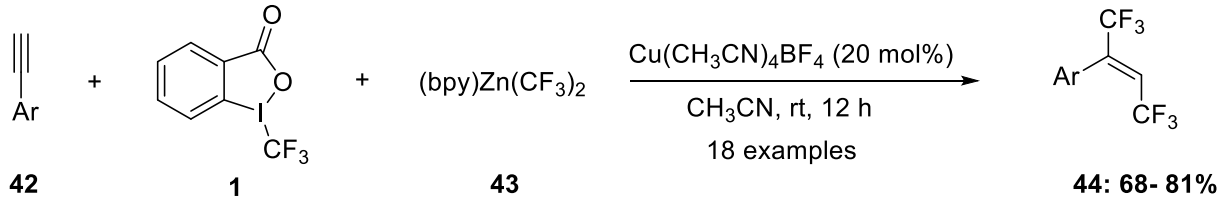


40 **2** **41: 46 - 90%**

R^1 = CF_3, CH_3, C_6H_5, I, R^2 = H, *p*-OMe, *p*-CH_3, *m*-CH_3, *p*-F, *p*-Cl, *p*-Br, *p*-CF_3, 2thiophene, n-butyl
R^3 = H, 7-CH_3, 5-OMe, 5-F, 4-Cl, 5-Cl, 5-Br

Scheme 14. Cu-catalysed cascade trifluoromethylation of alkyne **40** to CF_3 substituted spiro[cyclopentane-1,3'-indole] **41** using hypervalent iodine reagent **2.**

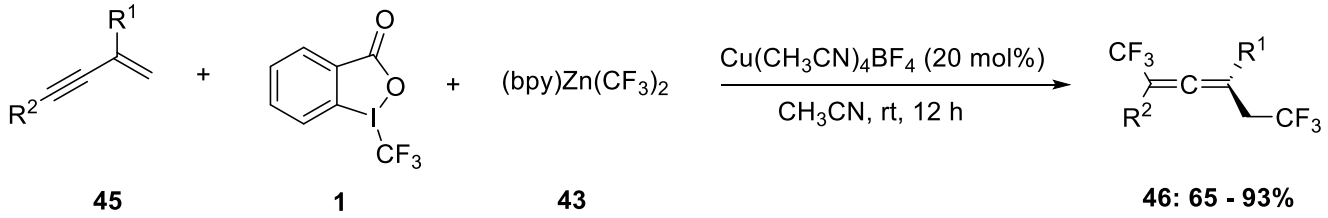
Recently Shen[106] et al presented the copper-catalyzed trifluoromethylation of alkenyl radicals, which allows easy bis(trifluoromethylation) of alkynes and 1,3-enynes under moderate conditions. In a model reaction, on combining hypervalent iodine reagent **1** (1.7 equiv) with 4-(tert-butyl)phenylacetylene **42** in presence of $Cu(CH_3CN)_4BF_4$ (20 mol %) and $(bpy)Zn(CF_3)_2$ **43** at room temperature yields product **44** in 81% yield with excellent stereoselectivity (E/Z > 95:5) (Scheme 15). No reaction was observed on using trifluoromethylating reagents such as Umemoto and Ruppert-Prakash reagent in CH_3CN at room temperature and if the reaction occurred the yield of the product was very low less than 10%. The protocol was found to be functional group tolerant. Arylacetylenes with electron-donating or electron-withdrawing group yield good to excellent corresponding 1,2 bis(trifluoromethylated) alkenes **44**. Complex molecules like alkynyl-containing steroids, carbohydrates, and vitamin E derivatives also provided corresponding bis trifluoromethylated products in moderate yield with high *E*-stereoselectivity (*E/Z* > 95:5). Alkynes substituted with a long alkyl chain gave a low yield with almost no stereoselectivity.



42 **1** **43** **44: 68- 81%**

Ar =*p*- ^{t}BuC_6H_4, *p*-PhC_6H_4, *p*-CNC_6H_4, *m,p*-diOMeC_6H_3, -O$(CH_2)_4CH_3$, QUI, PHE, dihydroindenone, 2-methylbenzothiazole,

Scheme 15. Copper-catalysed bis(trifluoromethylation) of alkynes **42** with Togni reagent **1** as CF_3 generator and $(bpy)Zn(CF_3)_2$ **43** to 1,2 bis(trifluoromethylated) alkenes **44**.



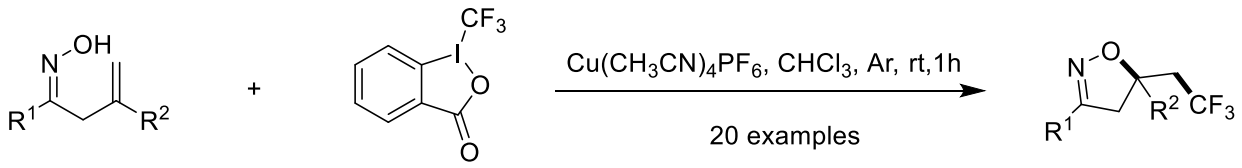
45 **1** **43** **46: 65 - 93%**

R^1 = H, CH_3, R^2 = *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-$COOMeC_6H_4$, fluoren-9-one, $BsO(CH_2)_2CH_2$,$PhthN(CH_2)_4$, $BzO(CH_2)_3$, 2-methoxynaphthalene,

Scheme 16. Cu-catalysed bis(trifluoromethylation) of 1,3-enynes **45** with trifluoromethylating reagent **1** to 1,4-bis(trifluoromethylated) allenes **46**.

Under the optimized condition 1,3 enynes **45** provide exclusively corresponding allenes **46** with no 1,2-addition side product. Both aryl and alkyl-substituted 1, 3 enynes gave moderate to good yield of corresponding product **46** (Scheme 16). To acquire a better understanding of the process of bis(trifluoromethylation) of alkynes and 1,3-enynes a radical capture experiment was carried out. On introducing a stoichiometric quantity of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to the arylalkyne under standard conditions, the yield of the intended product reduced to 27%, whereas TEMPO–CF_3 was formed in an 80% yield. This data revealed that the reaction involves a CF_3 radical in the reaction..

Xi-Tao Li et al[107] explored an efficient copper-catalyzed radical oxytrifluoromethylation reaction of alkenyl oximes under mild conditions. Substrate **47** was chosen as a starting material for screening the reaction with trifluoromethylating reagents **1** and **2** in presence of CuCl catalyst and ethyl acetate solvent but the desired product was obtained with a low yield. Different copper salts such as CuBr, CuI, $Cu(CH_3CN)_4PF_6$, CuOAc, and $Cu(OAc)_2$ were screened to see the effect on the yield of the reaction and it was observed that $Cu(CH_3CN)_4PF_6$ catalyst increased yield to 68%. Among ethyl acetate, chloroform, dioxane, and DCM; chloroform was found to be best in raising the yield of the product to 86%. Thus in the optimized reaction, on stirring substituted unsaturated oximes **47** dissolved in CH_3Cl with hypervalent iodine reagent **1** at room temp for 1 h in presence of $Cu(CH_3CN)_4PF_6$ catalyst the product **48** obtained were in good to excellent yield (Scheme 17).



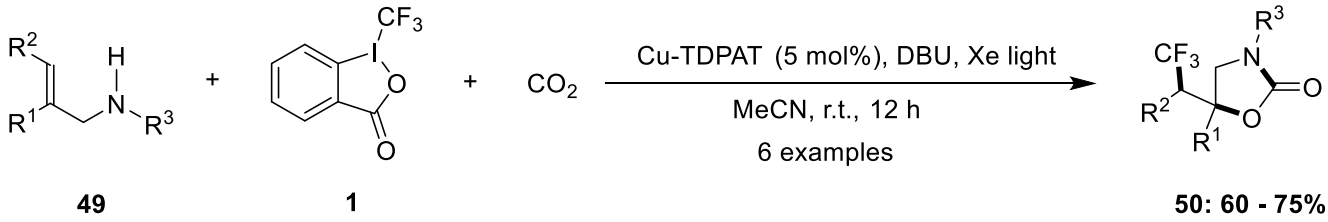
47 **1** **48: 81-91%**

R^1 = C_6H_5, *m*-$CH_3C_6H_4$, *m*-^{t}BuC_6H_4, *m*-BrC_6H_4, *m*-FC_6H_4 *p*-BrC_6H_4, *m*,-di$CH_3C_6H_3$, napthalene, thiophene; R^2 = C_6H_5, R_1 = C_6H_5, R_2 = *m*-$CH_3C_6H_4$, *m*-$OMeC_6H_4$, *m*-ClC_6H_4, *p*-IC_6H_4, *m*-$NO_2C_6H_4$, *m*-COOEt-C_6H_4, napthalene, thiophene, pyrimidine

Scheme 17. Cu-catalyzed oxytrifluoromethylation of alkenyl oximes **47** with hypervalent iodine reagent **1** to CF_3 containing isoxazolines **48**.

It was observed that the reaction occurred easily with a variety of oxime moiety. Various substituents at different positions on the phenyl ring, disubstituted phenyl, and polyarene naphthalene ring at R^1 and different electron donating and withdrawing substituents at phenyl ring, naphthalene ring or heterocycles such as pyrimidine and furan R^2 present at alkene substrates were all well tolerated and gave the corresponding products in good to excellent yield. The radical inhibition experiment by using 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) as a radical scavenger demonstrated that the reaction proceeds through the radical formation. The oxytrifluoromethylation process was significantly hindered, and TEMPO-CF_3 was produced at a yield of 21%.

Recently in 2020 Tiexin Zhang[108] and co-workers developed a procedure for merging CO_2 or CS_2 moiety with the CF_3 group in a single heterocyclic scaffold 2-oxazolidinone **50**, using Cu–TDPAT, a very durable Cu(II)-melamine coordination polymer a heterogeneous catalyst made from the melamine-based ligand H_6TDPAT and Cu(II) salt. In a probe reaction *N*-benzyl-2-phenylprop-2-en-1-amine **49** (1.0 equiv) was chosen as a substrate that reacts with hypervalent iodine reagent **1** (1.2 equiv) in presence of basic additive DBU (2.0 equiv), and a heterogeneous photocatalyst Cu–TDPAT (5 mol %) in acetonitrile under CO_2 atmosphere at room temperature to afford the desired trifluoromethylated 2-oxazolidone **50** product in good yield (Scheme 18). Xe light was selected as the light source.



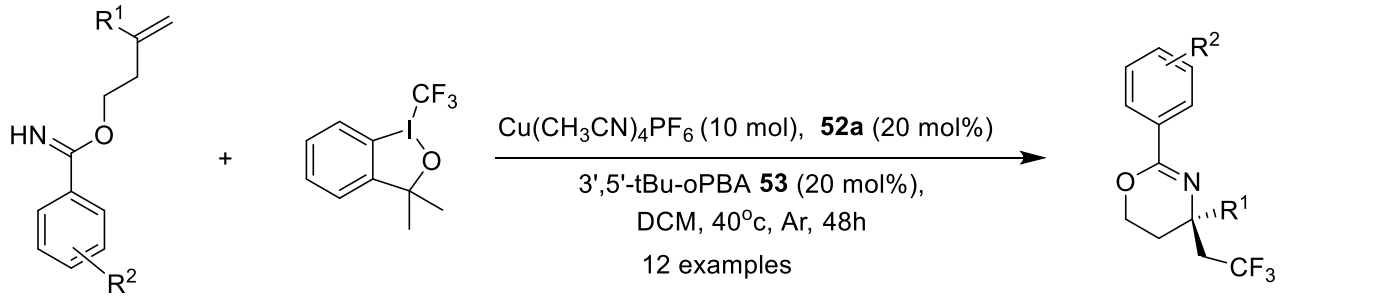
R^1 = C_6H_5, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-MeC_6H_4, 2-Nap; R^2 = Bn

Scheme 18. Photoswitchable Cu-catalysed oxytrifluoromethylation of allyamines **49** with Togni reagent **1** to trifluoromethylated 2-oxazolidinone **50.**

Control experiments revealed that the Cu-based coordination polymer, the basic additive, and light irradiation were all required for the reaction and on missing anyone, the product obtained was in traces. On evaluating different bases, it was found that inorganic bases were ineffective while among different organic bases DBU gave the best results. Various solvents such as DCM, DMF, CH_3CN, THF, and EtOH with different polarity and Cu (II) affinity were studied among which CH_3CN showed a high conversion to the product. On using ethanol as a solvent, it was observed that the activation of CO_2, allyl amine, and trifluoromethylating reagent was severely deteriorated due to the hydrogen bonding between ethanol and melamine moiety. A study of catalyst load showed that decreasing catalyst load from 5% to 2.5% makes reaction sluggish but doubling it to 10% does not show any significant improvement. The catalyst used in the reaction can be recovered just by filtering the reaction mixture and could be reused a minimum of 5 times without any negative effect on yield. The wavelength used in the reaction above 400 nm shows a significant increase in the yield of the product but beyond 455 nm very low yield was detected. Various substituted aromatic rings at allylamines were quite tolerant to the reaction. The substrate with a bulky endocyclic alkene moiety also produced corresponding spirocyclic products in good yield with high diastereoselectivity.

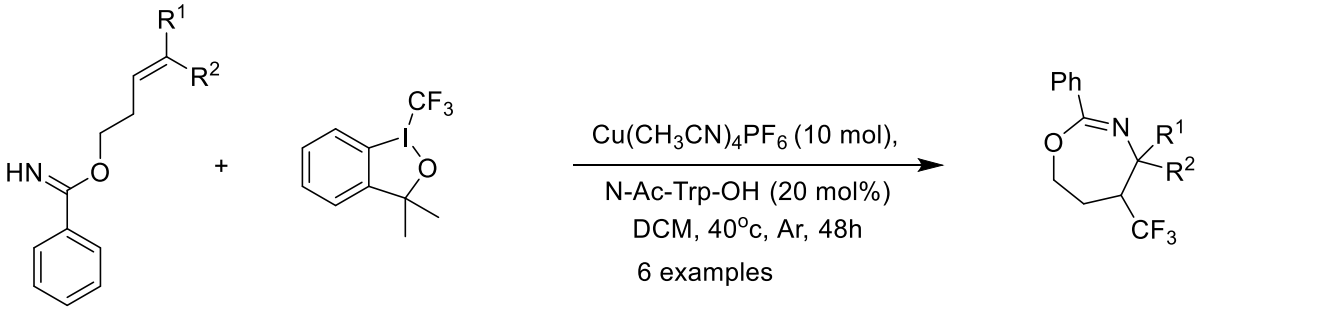
Functionalization of O-homoallyl benzimidate **51** using hypervalent iodine reagent **2** and $Cu(CH_3CN)_4PF_6$ as a catalyst in DCE (dichloroethane) at 45 °C for 24 – 48 h was reported by Xue-Qing Mou et al.[109] The chiral

1, 3-oxazines **54** with high enantioselectivity and racemic tetrahydro-1, 3-oxazepines **55** were obtained in the presence of a chiral BOX ligand **52a** (Figure 4). With these optimization conditions next, the substrate scope was explored with O-homoallyl benzimidates **51** with electron-donating or electron-withdrawing groups on the phenyl ring (Scheme 19), keeping the remaining conditions the same. All types of substituents including halogens were well endured throughout the reaction giving good yields (70-92%). Only the 2-Aryl-substituted alkene and gem-dimethyl substrate failed to produce satisfying results.



51 **2** **54 yield < 88%, ee < 95%**

R^1 = H, C_6H_5; R^2 = H, 4-OMe, 4-Me, 3-Me, 3,5-Me, 4-Cl, 4-Br, 4-I, 2 nap, 4-NO_2

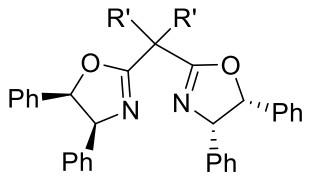


51 **2** **55 yield < 88%, ee < 95%**

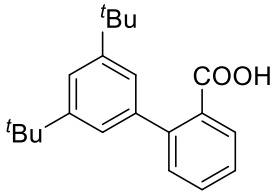
R^1 = H, Ph, 4-Br-Ph, 4-OMe-Ph, 3,4-OMe-Ph
R^2 = Ph, 4-Br-Ph, Me

Scheme 19. Cu-Catalyzed Enantioselective Intramolecular aminotrifluoromethylation of O- homoallyl benzimidate **51** with hypervalent iodine reagent **2** to CF_3 substituted 1,3-oxazines **54** and tetrahydro-1,3-oxazepine **55**.

Further benzimidate substrates equipped with 1,2-disubstituted alkene **51** reacted with Togni reagent **2** in presence of $Cu(CH_3CN)_4PF_6$ as catalyst and N-Ac-Trp-OH (N-alpha-Acetyl-L-tryptophan) in DCE yielded 7-membered tetrahydro-1,3-oxazepines **55** carrying CF_3 substituent with moderate to excellent diastereoselectivity (Scheme 19). 1,3 –oxazepines are commonly used in medicinal chemistry and material science. It is worth mentioning here that both benzimidate substrates equipped with E and Z alkenes gave the corresponding oxazepines with identical stereochemistry. In the substrate scope study, it was found that 1,1-diaryl-substituted substrates gave comparatively higher yields than 1,1-dialkyl-substituted substrates.



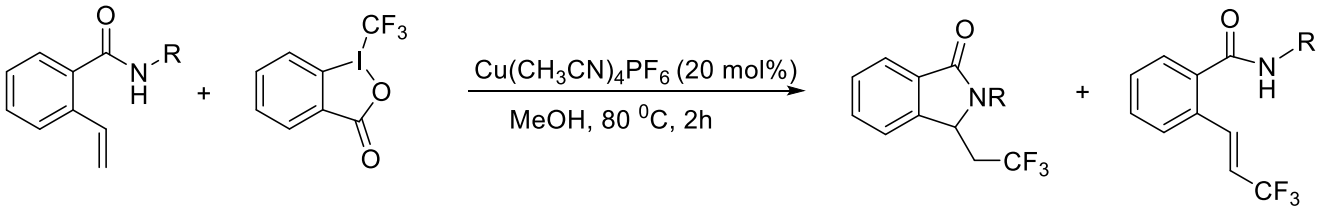
52a R'= [4-t-Bu-C_6H_4] 64%, 73%ee
52b R'= Me 55%, 43%ee
52c R'=Bn 56%, 68%ee
52d R'=H <5%, 28%ee



53 3',5'-^{t}Bu-oPBA

Figure 4. Various chiral BOX ligands **52** used for optimization of intramolecular aminotrifluoromethylation of O- homoallyl benzimidate **51**.

The aminotrifluoromethylated lactam products are valuable building blocks for drug development. An efficient copper-catalyzed aminotrifluoromethylation of alkenes followed by an intramolecular attack by nucleophilic amide to furnish a variety of CF_3-containing lactams is discussed here by Kun Shen and Qiu Wang.[110] The copper-catalyzed reactions of 2-vinylbenzamides **56** with different functional groups in presence of hypervalent iodine reagent **1** and methanol solvent at 80 °C temperature are explored. Two trifluoromethylated products **57** and **58** were obtained depending on protecting groups (Scheme 20). If the protecting group of amide is H, Ph, or Bn then product **58** was observed but with OMe protecting group cyclized product **57** was observed, suggesting the role of the alkoxy group in the radical cyclization step in the reaction mechanism .



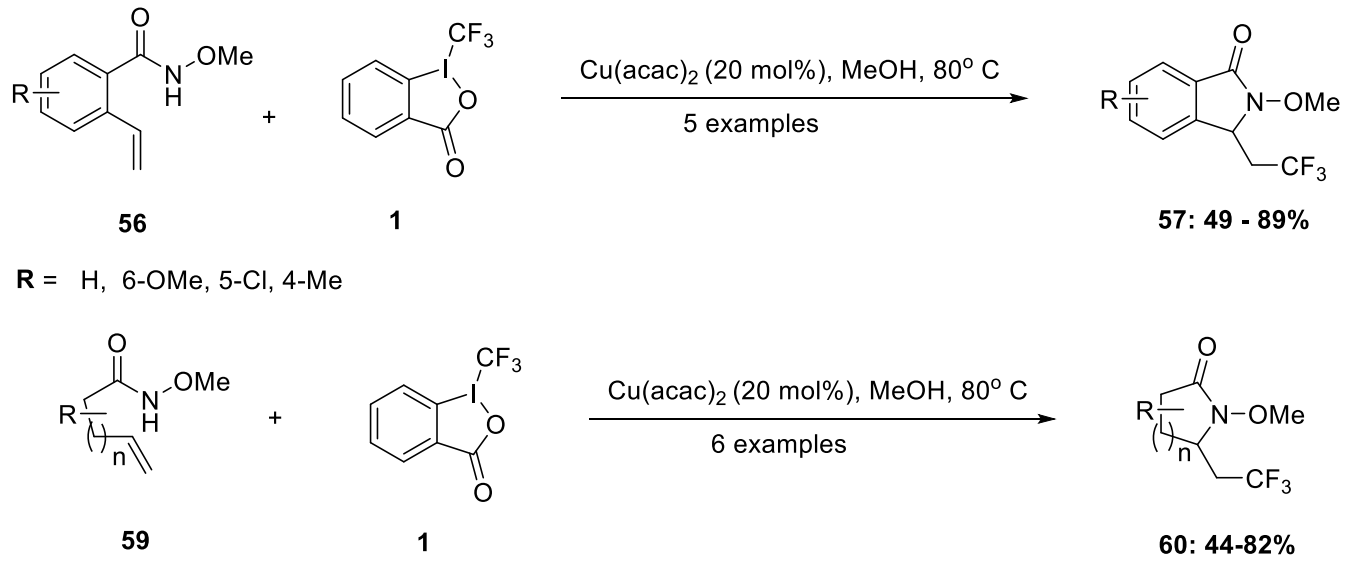
56 **1** **57: 79%** **58: 38-74%**

R= OMe, H, Ph, Bn

Scheme 20. Effect of N protecting group on the trifluoromethylation of 2-vinylbenzamides **56** with hypervalent iodine reagent **1.**

Further unactivated 2- allyl-N-methyoxybenzamide **56** were allowed to undergo the same reaction in presence of $Cu(acac)_2$ as a copper catalyst and it resulted in the formation of dihydroisoquinolione product **57.** Various N methoxybenzamides **59** also gave the expected product **60** in good yield (Scheme 21). The yield of the product was improved to 82% on using $Cu(acac)_2$ as a catalyst along with 2 equiv of hypervalent iodine reagent **1**. The detailed study of substrate scope showed that reaction was compatible with various electron-donating, withdrawing substituents, and sterically crowding ortho substituents on the aryl group. Along with these different substituents on the alkenyl chain also endured well through the reaction giving corresponding lactam products (Scheme 21). 1,1- disubstituted terminal alkenes unexpectedly gave oxytrifluoromethylation

products instead of aminotrifluoromethylation products. To prove the synthetic utility of the product it was further reduced to tetrahydroisoquinoline in two steps with 82% of yield.

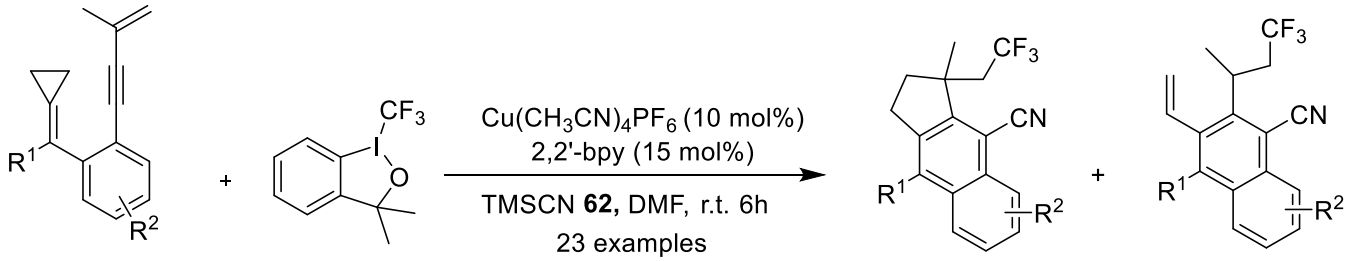


Scheme 21. Cu-catalyzed aminotrifluoromethylation of alkenes **56** and **59** using Hypervalent iodine reagent **1** to corresponding CF_3 substituted lactams **57** and **60**.

The cyclopenta[b]naphthalene derivatives, having trifluoromethyl and cyano groups can be used in pharmaceuticals, dyes, and liquid crystals. To synthesize difunctionalized cyclopenta[b]naphthalene derivatives M. Shi and their group tried the reaction between the alkylidenecyclopropanes (ACPs) with conjugated 1,3-enynes and hypervalent iodine reagent **2** in presence of Cu catalyst.[111] The synthesis of 3-trifluoroethyl-cyclopenta[b]naphthalene-4-carbonitrile derivatives proceed through copper-catalyzed difunctionalization of conjugated 1,3-enynes, followed by consecutive 6p-electrocyclization and finally vinyl cyclopropane rearrangement of allene type ACPs. The optimization conditions for the reaction are explored with 1,3-enyne-ACP (alkylidenecyclcoproanes) **61**, hypervalent iodine reagent **2**, trimethylsilyl cyanide (TMSCN) **62** as the starting materials, and it was found that reaction proceeds well in the presence of $Cu(CH_3CN)_4PF_6$ (10 mol %) as a copper catalyst, 2,2'-bipyridine (2,2'-bpy) (15 mol %) as a ligand and DMF solvent when stirred at room temperature for 6 h to yield the product **63** along with the side product **64** (Scheme 22).

Next, the substrate scope for the reaction was studied. The substrates with different alkyl groups, aryl groups, and halogen atoms at the 4' or 3' positions of the benzene ring endured well through the reaction giving 48%-66% yield. Along with this difunctionalization reactions of disubstituted 1,3-enyne-ACPs with –F or –Cl or two –Cl substituents proceed smoothly. When the monosubstituted ACP substrates were employed t in the reaction, then it was observed that an inseparable mixture of **63** and **64** was formed with a yield ranging from 80%-85% and a ratio ranging from 2:1 to 6:1.

Further, the reaction mechanism study reveals the formation of allenyl-Cu(III) species followed by 6p-electrocyclization of allene-ACP intermediate to give vinyl cyclopropane intermediate, which on rearrangement gives stable aromatic cyclopenta[b]naphthalene product.



61 **2** **63** **64**

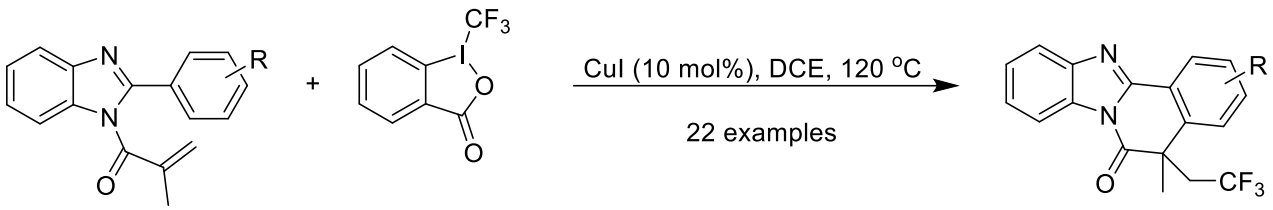
Yield: 77-84% ratio 2:1 - 6:1

R^1 = H, C_6H_5, 4-ClC_6H_4, 4-$^tBuC_6H_4$, 4-PhC_6H_4, 4-MeC_6H_4, 3-ClC_6H_4, 3-MeC_6H_4, 2-FC_6H_4, 2-ClC_6H_4
R^2 = H, 5-Cl, 6-F, 3-Cl, 5-CF_3, 5-F, 4-Me, OMe, 1, 3 benzodioxole

Scheme 22. Cu-catalyzed addition-cycloisomerization difunctionalization reaction of 1,3-enyne-(alkylidenecyclcoproanes) **61** with Togni reagent **2** and TMSCN **62** to 3-trifluoroethylcyclopenta[*b*]naphthalene-4-carbonitrile derivatives **63** and **64**.

Recently in 2021, the copper catalyzed synthesis of CF_3-containing tetracyclic core benzimidazo[2,1-a]isoquinolin-6(5H)-ones using Togni reagent is discussed by Kai Sun et al.[112] The reaction follows a radical pathway in which Togni reagent is activated by a copper catalyst. N-methacryloyl-2-phenylbenzoimidazole **65** is used as a substrate for model reaction. Screening of different catalysts proved CuI to be better over CuBr, CuCl or $Cu(OAc)_2$. While among the different solvents screened like PhCl, EtOAc, DCM, DCE, DMSO, and DMF, only dichloroethane (DCE) was found to be effective. Optimization conditions were set as CuI catalyst (10 mol %), Togni reagent **1** (2.0 equiv.) as the CF_3 source, in presence of DCE at 120 °C for 0.5 h to obtain product **66** (Scheme 23).

It was also proved that the methyl group attached to the double bond of acrylamide plays an important role in cyclization. With these optimization conditions in hand, further substrate scope for the reaction was explored. It was observed that both electron donating as well as electron withdrawing substituents including Me, OMe, OBn, COOMe, CN, CF_3, F, Cl, and Br were tolerated well through the reaction except NO_2. Even the sterically crowded multisubstituted substrates such as naphthyl endured well. Along with this thiophene and pyridine containing heteroaryl products were also synthesized with moderate 53% and 56% yields. When 1-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1H-benzo[d]imidazol-1-yl)prop-2-en-1-one was used as a substrate, two isomers were obtained with a 1.4 : 1 molar ratio. To prove the synthetic utility, the scale up reaction was also performed successfully.



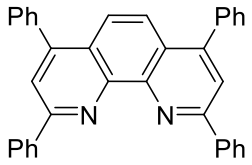
65 **1** **66: 53 - 79%**

R = H, 4-OMe, 4-Me, 4-OBn, 2-OMe, 2-Me, 3-CH_3, 4-COOMe, 4-CF_3, 4-F, 4-Cl, 4-Br, 2-F, 3-Cl, 2,4-CH_3, 2,4-Cl, 3,5-Cl

Scheme 23. Cu-catalyzed radical cascade carbocyclization reaction of 2-arylbenzoimidazoles **65** with hypervalent iodine reagent **1** to CF_3-containing tetracyclic core benzimidazo[2,1-*a*]iso-quinolin-6(5*H*)-one **66**.

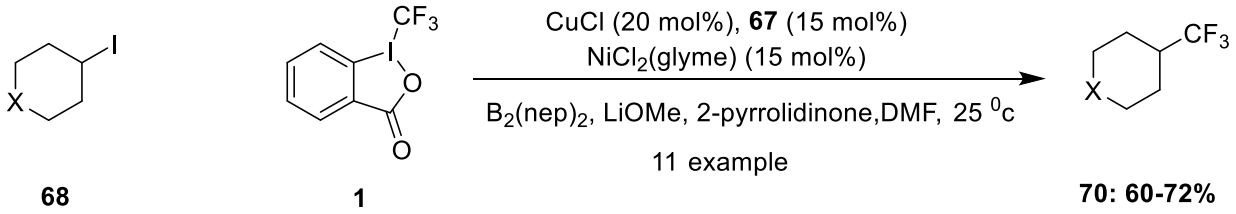
The reductive cross–electrophile coupling of alkyl iodides **68/69** and electrophilic CF_3 species generated from hypervalent iodine reagent and Cu catalyst to give **70** and **71** was explored by Yanchi et. al.[113] Exploration of reaction optimization revealed that along with CuCl catalyst use of ligand **67** (figure 5), promoter $NiCl_2$ glyme, additive 2-pyrrolidinone, terminal reductant $B_2(nep)_2$/LiOMe and DMF solvent helped in increasing efficiency of the reaction. Optimization results emphasized the use of Ni promoter and ligand **67.** Without $B_2(nep)_2$ i.e. bis(neopentyl glyxolato)diboron, no product was observed while eliminating LiOMe resulted in poor yield. Other trifluromethylating compounds like Umemoto's reagent, Ruppert reagent, and Togni reagent **2** were ineffective.

These optimization results were further extended from primary halides to secondary halides, cyclic four, five, and six-membered rings, acyclic alkyl iodides and proved efficient with moderate yields. Primary and secondary alkyl halides tethered to esters and ethers also provided moderate to good product yield. The reaction was compatible with Boc, secondary amine, phthalimide, ester, acetal, silyl, thiophenyl, furyl, and easily accessible free amine and aryl bromide groups (Scheme 24).



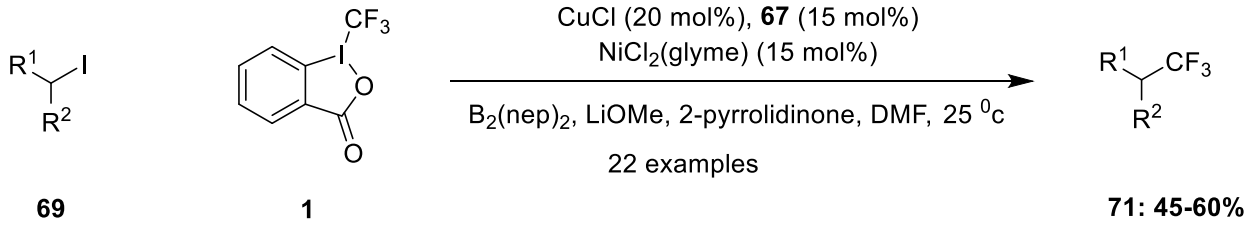
67

Figure 5. Ligand involved with cu-catalyst in reductive trifluoromethylation of alkyl iodide **68.**



68 **1** **70: 60-72%**

X = N-R; R = Cbz, Boc,*p*-MeOC$_6$H$_4$CO, *o*-Br, *p*-NHCbz
X = C-R; R = TBDPSO,1,3-dioxolane

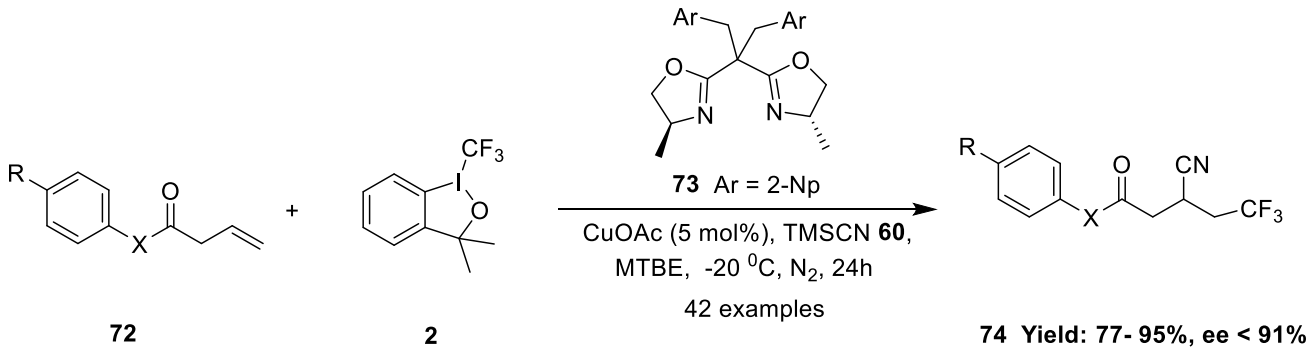


69 **1** **71: 45-60%**

R^1=Me, H; R^2 = $(CH_2)_2OC(O)C_6H_4OMe$, TBDPSO-$(CH_2)_2$,
$(CH_2)_2OC(O)C_4H_3S$, $(CH_2)_2OC(O)C_4H_3O$;$(CH_2)_2C_6H_4OMe$,
$(CH_2)_2$benzodioxole, methylisoindoline-1,3dione
TBDPSO$(CH_2)_4$,$CH_2CH_2OC(O)C_6H_4OMe$,
BnOC(O)$(CH_2)_4$, $PhOCH_2CH_2$, $TsNHCH_2CH_2$

Scheme 24. Cu-catalysed reductive trifluoromethylation of alkyl iodide **68/69** in presence of hypervalent iodine **1** reagent as CF_3 source.

Asymmetric radical cyanation provides an efficient pathway for synthesizing optically pure nitriles, an essential part of bioactive materials and synthetically useful synthons. Enantioselective cyanation of carbon-centered radical facilitated by Togni reagent is reported here by Zohu and coworkers.[114] The desired enantiomeric excess is achieved by adding a chelating group with an alkene. Considering the fact that, alkyl-substituted terminal alkenes bearing a carbonyl group at the β position are potential substrates for the synthesis, substrate **72** was treated with 5 mol % CuOAc, and 6 mol % chiral bisoxazoline (Box) ligands as catalysts in the presence of TMSCN **62** and hypervalent iodine reagent **2** in CH_3CN to get desired product. Screening of solvents and ligands proved (MTBE) methyl tert-butyl ether as a better solvent and Ligand **73** bearing gem-dinaphthyls as a better ligand which improved the yield of the product **74** to 93% yield with excellent enantioselectivity (90% ee) as shown in the scheme 25.

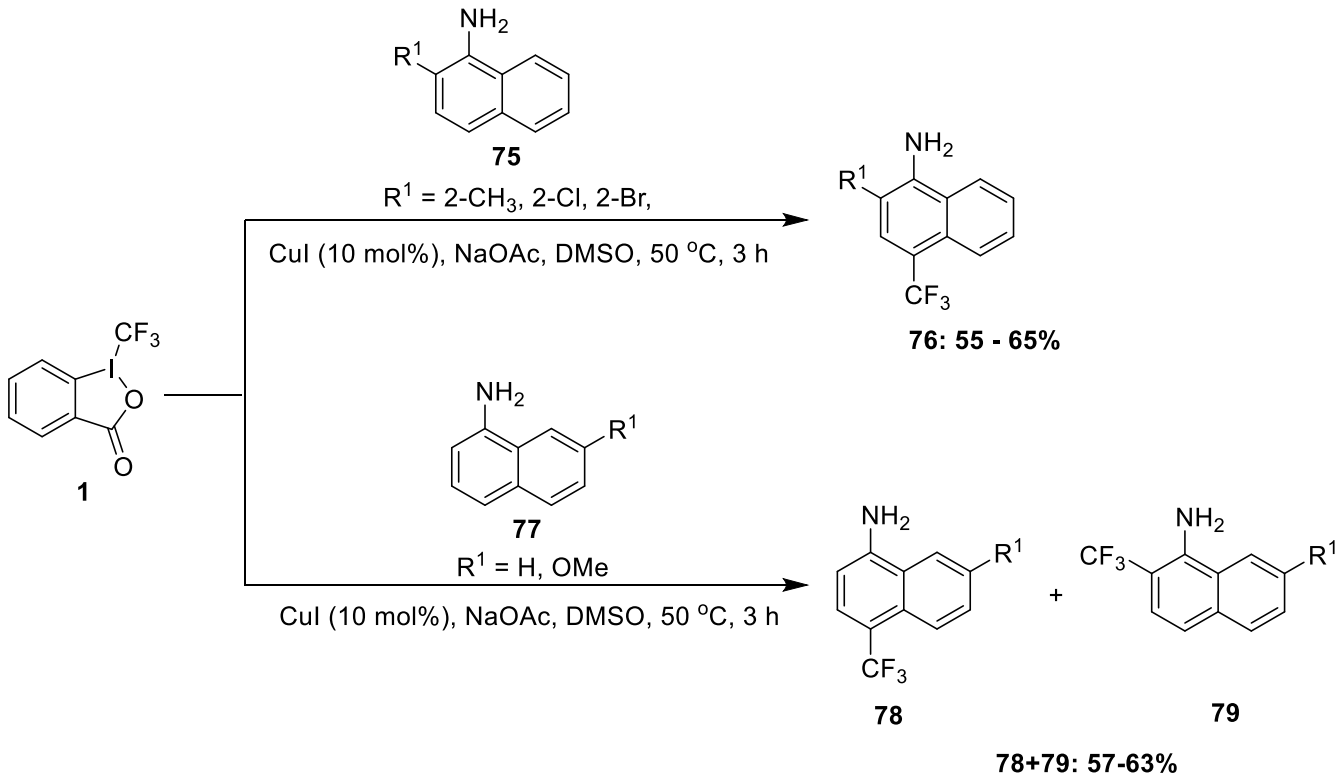


X = C, N, O
R= ^{t}Bu, H, OMe, Me, Ph, F, Cl, CF_3, CN, OAc,

Scheme 25. Cu-catalyzed enantioselective cyanation and trifluoromethylation of alkyl-substituted alkenes **72** facilitated by Togni reagent **2.**

A substrate study showed that the presence of both electron-donating and electron-withdrawing groups such as ^{t}Bu, OMe, Me, Ph, F, Cl, and CF_3 at the C_2 and/or C_4 positions on the benzene ring of benzyl allyl ketones resulted in good yields (80%−95%) and good enantioselectivities (81%−90%). Various electron donating substituents increased enantioselectivity. Reaction was successful with a naphthalene-derived system and aromatic rings with synthetically useful handles affording moderate to good yields (67%−93%) and moderate to good enantioselectivities (70%−84% ee). Along with simple ketones, esters and primary and secondary alkyl amides with an array of functional groups on the aromatic ring were effective with good yields and enantioselectivities. N-aryl amide derived from ortho-methoxy aniline and amides derived from N-ethylaniline were less effective. The ester substrates obtained from complex bioactive Mecarbinate and Estrone also resulted in desired products in 50% yield (81% ee) and 72% yield (81%de), respectively. To gain an insight into the role of the carbonyl group as a chelating agent in the mechanism pathway, certain experiments were carried out. It was observed that as the length of the carbon chain between the carbonyl group and alkene increases, enantioselectivity drastically decreases from 80% to 17%. Also, substrates without the carbonyl group resulted in poor enantioselectivity. This proved the chelating effect of the carbonyl groups plays an important role in the radical coupling with chiral copper cyanides.

Primary aryl amines especially naphthyl amines are important motifs in pharmaceuticals, agrochemicals, and dyes. To achieve the goal of the introduction of the CF_3 functional group across naphthyl amines, Chunfeng Jing et al[115] reported the Cu catalyzed reaction of 1-naphthylamines **75** with hypervalent iodine reagent **1** in presence of NaOAc and DMSO at 50 ^{0}C for 3h to yield product **76**. The *p*-CF_3 substituted products were obtained with moderate to good yields when the ortho position is blocked. With free ortho position, e.g. **77,** mixtures of 2-CF_3 and 4- CF_3 substituted products were obtained with the para-substituted product as a dominant regioisomer **78** and **79** (Scheme: 26).

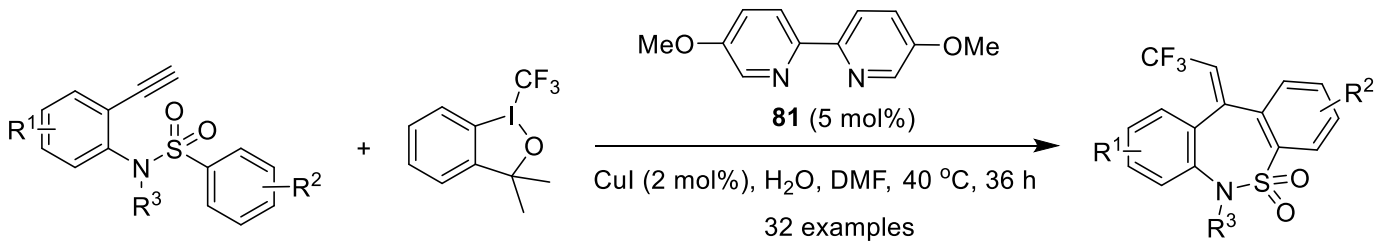


Scheme 26. Cu- catalyzed trifluoromethylation of 1-napthylamine **75/77** in presence of hypervalent iodine reagent **1** to CF3 substituted 1-napthylamine **76, 78, 79**.

The 7-membered cyclic sulfonamide, the dioxodibenzothiazepines are important motifs in sulfonamide drug molecules viz. antidepressant drugs tianeptine and zepastine. These molecules also exhibit anticancer activity. The radical cyclization reactions with alkynes have the advantages of high regioselectivity and efficiency due to in situ formation of vinyl radical which can induce further cascade reactions.

To synthesize dioxodibenzothiazepines **82** a Cu-catalyzed radical strategy involving trifluoromethylation of terminal alkyne present in substrate N-(2-ethynylphenyl)-N-isopropyl-4methylbenzenesulfonamide **80** using Togni reagent **2** followed by cyclization was developed by Zi-Qi Zhang et al.[116]. A detailed study of optimization conditions was further carried out with the use of CuI (2 mol %), the electron-rich ligand 5,5′-dimethoxy-2,2′-Bipyridine **81** (2 mol %) in DMF at 40 ^{0}C improved the yield (Scheme 27). Further addition of 1 equiv of water was found to be positively affecting the yield of a reaction.

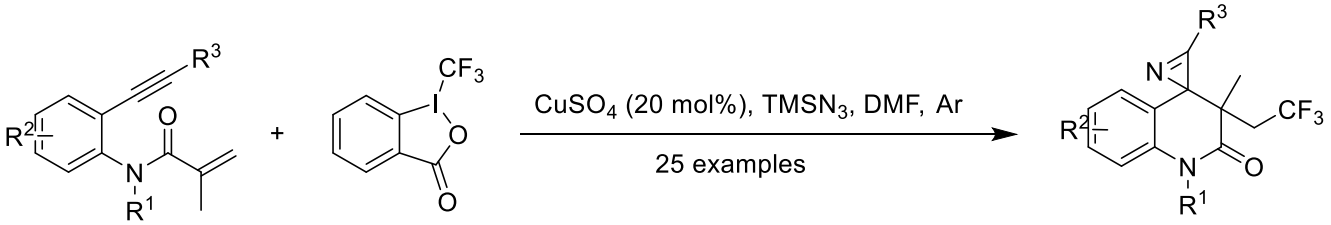
An array of functional groups on the phenyl ring was well tolerated. It was observed that the para-electron-donating group delivered the products at a slightly lower yield while para-electron-withdrawing groups such as trifluoromethyl and cyano gave good yields. Ortho-bromine substituted substrate gave the product with E/Z selectivity of 7:1, while *o*-chlorine-substituted gave only E product. Electron donating groups such as alkyl, and alkoxy on the arylalkyne ring and electron withdrawing substituents (R^1) such as F, Cl, Br, esters, and cyano were well tolerated. Ortho substituted products resulted in lower efficiency, improved by increasing the catalyst loading to 3% and replacing the ligand with 6% DMAP. N-protecting groups such as cyclohexyl, Bz, Boc, and Piv also endured well in this reaction.



R^1 = H, *o*-Me, *o*-*F,* *o*-Cl, *o*-Br, *o*-OMe, *o*-CN, *m*-Me, *m*-F, *m*-Cl, *m*-Br, *m*-COOMe; R^2 = ^{i}Pr, R_2 = Bz, Boc, Me, Cy; R^3 = H, *o*-Me, *o*-^{t}Bu, *o*-Ph, *o*-F, *o*-Cl, *o*-Br, *o*-CF_3, *o*-CN, *o*-OCF_3, *p*-Cl, *p*-Br

Scheme 27. Cu-catalyzed trifluoromethylation/cyclization of alkynes **80** utilizing hypervalent iodine reagent **2** to dioxodibenzothiazepines **82.**

Scaffolds containing 3,4-dihydroquinolin-2(1H)-ones and 2H-azirines are an imperative part of many bioactive natural products and drugs. Construction of these structurally important heterocyclic scaffolds via radical cyclization was discussed by Meng et al.[117] The reaction of benzene-linked 1,7-enynes **83** (0.2 mmol) with aminating reagent $TMSN_3$ (0.5 mmol) and Togni reagent **1** (0.5 mmol) in DMF using 20 mol % $CuSO_4$ as the catalyst for 5 h at 60 °C resulted in the formation of product **84** (Scheme 28). Various solvents like DMSO, CH_3CN, and toluene did not give satisfactory yields like DMF. During the optimization process, various copper salts such as CuBr, CuI, CuCN, $Cu(OAc)_2$, $Cu(OTf)_2$, $CuCl_2$, and $CuSO_4$ were investigated, among which $CuSO_4$ was most efficient. To study the scope of this cyclization reaction, different substituents on the phenyl ring of aniline derivatives like CH_3, F, Cl, Br, and multiple substituents like 2,4 dimethyl were investigated and well-tolerated. Various N-protecting groups, such as N-isopropyl, N-Bn, N-Ms, N-SO_2Ph, N- $SO_2C_6H_4Cl$-*m*, N-$SO_2C_6H_4Cl$-*p*, N-$SO_2C_6H_4Me$-*o*, N-Ts, and N-2-naphthalenylsulfonyl were also well-tolerated to give good yields. However, no product was observed with N-unprotected amide, phenyl-substituted alkene substrate, and unsubstituted allylic substrate. The effect of substituents on the phenyl ring in the terminal alkyne was explored, and substituents such as *p*-MeO, *p*-Me, *p*-^{t}Bu, *p*-Cl, and *p*-phenyl were well endured. It is important to note here that when benzene-linked 1,6-enyne is used as a substrate, no formation of desired product was observed as the product involves a less stable 5 membered ring attached to aziridine.



83 **1** **84: 55- 88%**

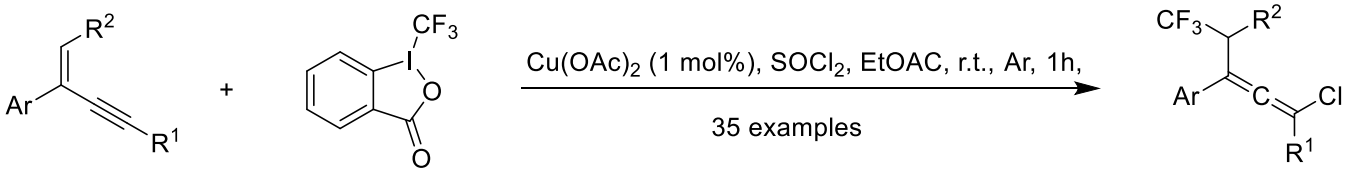
R^1 = CH_3, $CH(CH_3)_2$, Bn, Ms, $SO_2C_6H_5$, Ts, $SO_2C_6H_3Cl$-*m,* $SO_2C_6H_3Cl$-*p,* $SO_2C_6H_3Me$-*o;* R^2 = H, *p*-CH_3, *p*-F, *p*-Cl, *p*-Br; R^3 = C_6H_5, *p*-$OMeC_6H_4$, *p*-MeC_6H_4, *p*-ClC_6H_4, $CH_2(CH_2)_3CH_3$

Scheme 28. Cu-catalysed cyclization of 1,7-enynes **83** to trifluoromethyl-containing 1'H-spiro[azirine-2,4'-quinolin]-2'(3'H)-ones **84** using Togni reagent **1**.

Chlorinated allenes are useful intermediates and versatile building blocks in organic synthesis. The facile synthesis of halo and CF_3 containing tetrasubstituted allene derivatives with high regioselectivity is discussed in this reaction.[119] The reaction of 1,3-enynes **85** with a nucleophilic halide reagent (SOX_2) and an electrophilic CF_3 reagent in presence of Cu-catalyst resulted in the formation of synthetically important allene derivatives **86** (Scheme 29). During the optimization study, 1,3-enynes was reacted with Togni reagent **1** in presence of $SOCl_2$ at R.T. under argon atm. and various Cu catalysts and solvents were screened. The results showed $Cu(OAc)_2$ as an efficient catalyst over $CuCl_2$, Cu_2O, and CuI, and EtOAc as an efficient solvent.

Next, the substrate scope of 1,3-enynes derived from different alkenyl moieties was carried out. The alkenyl moiety having various substituents such as F, Cl, and Br at the para position of benzene ring gave the products 80−87% yields and methyl or halide group at the meta position of benzene ring gave good to excellent yields 77−92%. Even the sterically hindered ortho-substituted aryl group on alkenyl moiety was well tolerated to give 73−98% yields. Disubstituted benzene rings, and fused ring-derived 1, 3-enynes were well endured through reaction. 1, 3-enynes incorporated with L-menthol, polyethylene glycol (PEG), propofol, and vitamin E gave products with good yields. When aliphatic alkynes such as propyl, cyclopropyl, tert-butyl, and n-hexyl were employed as substrates in the reaction, the results were satisfactory.

Further synthetic applications of the products were showcased by converting chlorine group into synthetically useful groups such as SCN, Ph, and H by using KSCN; Pd $(PPh_3)_2Cl_2$, Cs_2CO_3, $PhB(OH)_2$; and Zn respectively.



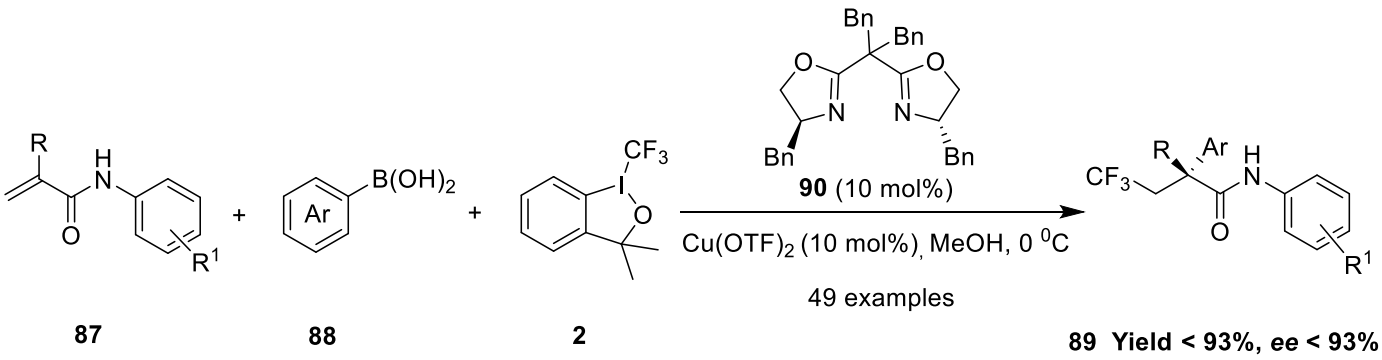
85 **1** **86: 60%- 92%**

Ar = Ph, R^1 = Ph, 4-FPh, 4-ClPh, 4-BrPh, 3-MePh,
3-FPh, 3-ClPh, 3-BrPh, 2-MePh, 2-FPh, 2-ClPh,
2-BrPh, 2,5-diMe-Ph, 1-naphthyl, 2-naphthyl, R^2 = H, Et

Scheme 29. Copper-catalyzed 1,4-chloro trifluoromethylation of 1,3-enynes **85** using Togni reagent **1** to CF_3-containing tetrasubstituted allene **86.**

A straightforward, facile asymmetric copper-catalyzed trifluoromethyl-arylation of α-substituted acrylamides was reported by Lianqian Wu and coworkers.[120] When the substituted acrylamides **87** and Aryl boronic acids **88** were reacted with Togni reagent **2** in presence of Box ligand and Cu catalyst, an amide product **89** with chiral quaternary α carbon atom was formed with higher enantioselectivity (Scheme 30). For optimization of the reaction, various alkenes bearing different carbonyl groups were chosen viz. phenyl ketone, methyl esters, and secondary and tertiary amides. Among different substrates, tertiary amides were found to be effective. To improve the yield and enantioselectivity, the reaction was carried out in presence of various Box ligands and ligand **90** was found to be the most efficient. Screening of solvents and different Cu catalysts proved methanol as a better solvent and $Cu(OTf)_2$ as the best catalyst. It is important to note here that the reaction did not work without the carbonyl group e.g. α-methylstyrene. Next to improve the enantioselectivity of the reaction, various electron rich and electron deficient aryl boronic acids were employed in the reaction.

The various aryl boronic acids with electron withdrawing or donating substituents or with heteroaryl groups gave excellent enantioselectivity and yield. The substituted acrylamides with various aryl and alkyl groups at the α-carbon position endured well through the reaction to give products with moderate to excellent yields and excellent enantioselectivities (85%-97%). Various heteroaryl boronic acids, such as benzothiophene, pyridine, and pyrimidine, were also suitable for the reaction giving desired products with (88−96% ee). Acrylamides with different aryl groups at the α-carbon position endured well to give coupled products with excellent enantioselectivities (89−98% ee). Both aryl and alkyl N-substituted amides worked well in the reaction. Next, acrylamides bearing different alkyl groups at the α-position like, *n*Pr, -CH_2OH, -CH_2OMe, etc. worked well to give desired products in moderate to good yields.



R = H, Me, Ph, n-Pr, CH_2-CH_2-OH, CH_2-CH_2-OMe;
R^1 = H, 3-F, 3,5-diCH_3, 4-OMe, 3, 5-diBr;
Ar = 4-tBu, 4-Me, 3-Me, 3-Ph, 4-OPh, 4-SMe, 4-Br
4-OCF_3, 2-F, 4-Ac, 4-CN, 4-COOMe, 4-CF_3, 3-NO_2,
4-SO_2Me, 3,4-diCl, 3,5-diF, 2-Nap, benzothiophene

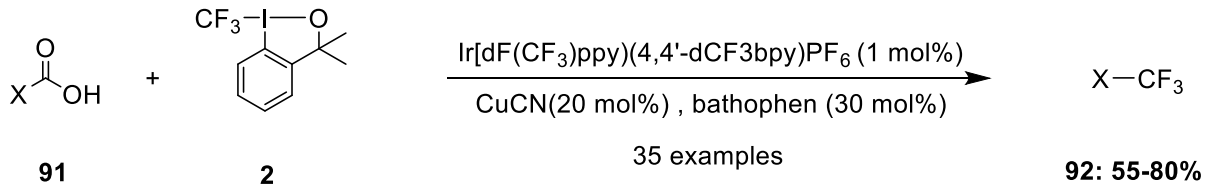
Scheme 30. Enantioselective Cu-catalyzed arylation of tertiary carbon-centered radicals using hypervalent iodine reagent **2.**

It is important to note here that, the reactions were limited to the terminal alkenes, and very poor or no yields were obtained with β-substituted internal alkene or with bulky alkyl group at the α-position. Further to prove the utility of the product, the amide was converted to corresponding alcohol, amine, or allowed to undergo cyclization to give lactam product. In the mechanism study, the involvement of benzylic radical in the reaction was proved by using a CBr_4 radical scavenger. The benzylic radicals formed by ketones or esters did not result in expected products due to reductive elimination of Cu(III) and self-coupling respectively, hence reactions with these substrates failed to give products. Further to explore synthetic applications of the products the amide functional group was successfully converted into corresponding alcohol using NaH and LAH, to amine using $BH_3.Me_2S$, simple primary amide using CAN and oxindole using LiH.

The copper-catalyzed decarboxylative trifluoromethylation of aliphatic carboxylic acids, which follows the photoredox catalytic pathway was reported by W. C. MacMillan et al.[121] The photoexcitation of the Ir(III) photocatalyst Ir[dF(CF_3)ppy]$_2$(4,4′-dCF_3bpy)PF_6 with visible light was carried out and the highly oxidizing excited-state *Ir(III) (E1/2 red [*Ir(III)/Ir(II)] = 1.65 V vs SCE in MeCN) was obtained. This further helped to remove CO_2 from the molecule by providing an electron initiating SET mechanism. Intermediate formed with the help of Ir(III) photocatalyst further interacts with hypervalent iodine reagent **2** to give trifluoromethylated product. Further, this Ir(III) photoredox was employed for the optimization reaction of 1-benzoylpiperidine-4-carboxylic acid as a model substrate. Various electrophilic trifluoromethyl sources such as Umemoto reagent, Togni reagent **1**, and Togni reagent **2** were employed in reaction and among all Togni reagent **2** gave better results. Among the various Cu catalysts screened, CuCN was found superior over $CuCl_2$. The use of ligand bathophenanthroline (30 mol%) and Barton's base (2-tertbutyl-1,1,3,3-tetramethylguanidine, BTMG) in ethyl acetate solvent was found to be most effective.

Screening of substrates **91** showed that reaction worked well with primary, secondary as well as tertiary carboxylic acids with moderate to excellent product **92** yields (Scheme 31). Phenylacetic acids were found to be effective with an array of functional groups on the aryl ring, including electron-withdrawing (70–80% yield), electron-donating (74% yield), and electron-neutral substituents (60 and 70% yield, respectively). Various boronic esters, aryl bromides, and heterocycles including ortho-ortho-disubstituted

heterocycles tolerated the reaction conditions. A variety of non-benzylic primary acids also resulted in desired products with 31−82% yield. Amongst the secondary and tertiary carboxylic acids, cyclic carboxylic acids, including strained 3- and 4-membered ring showed 45−93% yield, and different bicyclic and spirocyclic also resulted in desired products with good yields. Further to demonstrate the synthetic utility of the reaction, a large number of medicinal agents and natural products were converted chemoselectively into trifluoromethylated derivatives with satisfactory yield.

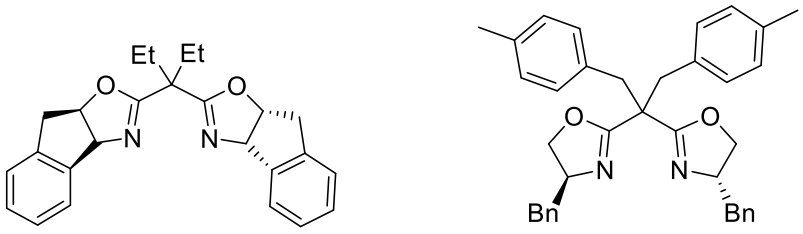


91 **2** **92: 55-80%**

Primary carboxylic acids
X = $(CH_2)_n$-R
n= 1, 2, R= 4-F-Ph, 3-Br-Ph, 3-CN-Ph ,4-CF_3-Ph, 2-OMe-Ph, 4-BPin-Ph, 2Nap, 3-pyridyl' 5 pyrimidyl, 3-thiophenyl, [1,2,4]triazolo[1,5-a]pyrimidyl, Ph, pyridyl, imidazole, 1-adamantyl, cyclohxyl-NBoc
Secondary carboxylic acids
X = Boc-piperidine, *p*-CF_3-Ph-CO-piperidyl, 2-NBoc-cycylohexyl,3-azetidine(Boc) cyclopropyl

Scheme 31. Cu-catalysed decarboxylative trifluoromethylation of aliphatic carboxylic acid **91** using hypervalent iodine reagent **2**.

Optically pure amines and amides are commonly used functional groups as synthons and also they are part of natural products. Synthesis of a variety of enantioenriched amides bearing pharmaceutically important triflorormethyl group is reported here by Guoyu Zhang et al.[122] The reaction of N-vinyl benzamide **95** and TMSCN **62** with Togni reagent **1** to give **96** is considered as a model reaction here in scheme 32. Different Cu catalysts, Box ligands and solvents were screened for the reaction and it was concluded that reaction works well with CuOAc catalyst, Box ligand **94** (figure 6) and MTBE solvent.

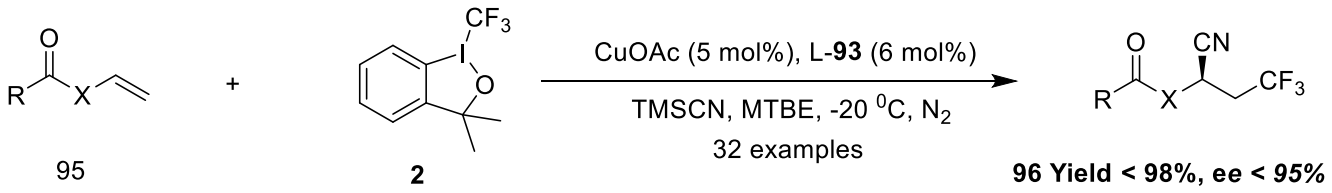


93 **94**

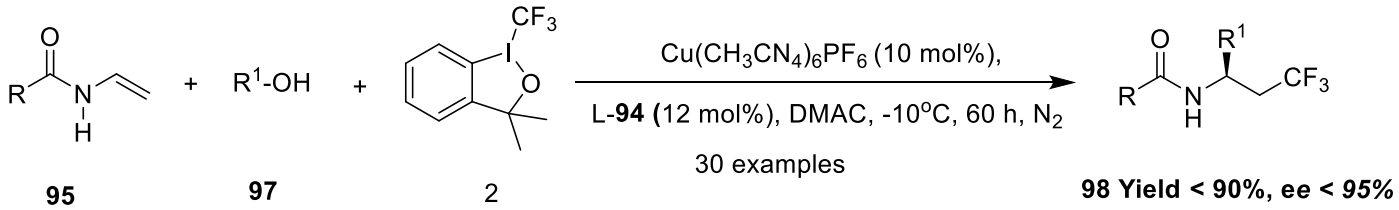
Figure 6. Box ligand screened for the asymmetric cyanation and etherification of enamides.

After the reaction conditions are set, substrate scope study was done. Several benzyl substituted N-Vinyl benzamides afforded the products with excellent yields (85%- 98%) and excellent enantioselectivities (92%-98% ee). The reaction of N-vinyl-amides with 1- or 2-naphthalenyl groups gave 90%- 93% yield (93%-92%

ee). Substrates derived from alkyl carboxylic acids, N-vinyl Boc-amides endured well in the reaction. But β-substitued N-vinyl amides as substrate failed to give corresponding tetrasubstituted product.



X = NH, N-Ph,N-Boc,O, phthalic anhydride, pyrrolidin-2-one
R = Ph, 4-OMe-Ph, 4-CF_3 -Ph, 4- Ph-Ph, 3-Me -Ph, 2-Me -Ph,
3,5 diCF_3, 2- Nap, 1-Nap, Ph-CH_2, Ph-$(CH_2)_2$, Boc, Furyl, Thiophyl,
4-Cl-pyridyl, Thiophene-CH_2, 3-CF_3-indole, p-toluene-sulfonyl



R^1 = OMe, OEt, OPr^n, OC_5H_{11}, OBn, -$(CH_2)_2$OH.
R = Ph, 4-OMe-Ph, 4-PH-Ph, 4-Cl-Ph, 4-COOMe-Ph, 4CN-Ph, 4-CF_3-Ph, 4-SCF_3-Ph, 2-Me-Ph, 3-Me-Ph, 2-Nap, 1-Nap, Furan,

Scheme 32. Cu-catalyzed asymmetric cyanation and etherification of enamides **95** in presence of hypervalent iodine reagent **2** the CF_3 source**.**

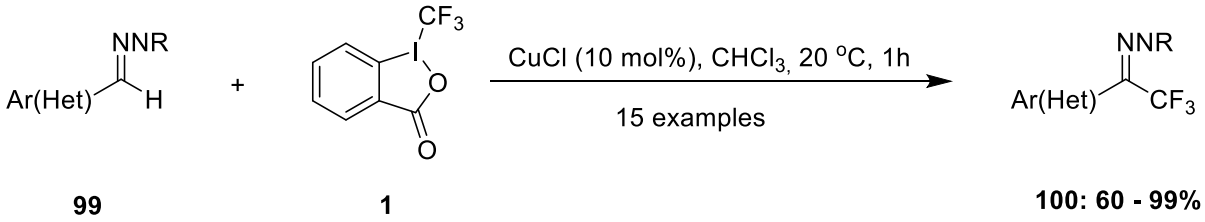
As the properties of the intermediate formed in the reaction i.e. carbon-centered radical adjacent to nitrogen (CRAN) and carbon-centered radical adjacent to oxygen are the same, the asymmetric trifluoromethylcyanation reaction of ester was investigated and a series of enantioenriched α-cyano esters were successfully synthesized. Further screening of substrates revealed that both vinyl aryl esters and vinyl alkyl esters gave corresponding products in good to excellent yields (70-99%) with excellent enantioselectivities (87-91% ee). Notably, high functional group tolerance was observed for the reaction. Substrates bearing heterocycles such as indole and thiophene also endured well.

Next, testing of the asymmetric coupling of CRAN with alcohols was done using $(MeO)_4Si$ instead of TMSCN. The reaction of enamide **95** with Togni reagent, $(MeO)_4Si$, Ligand **93,** and 10 mol % $Cu(CH_3CN)_4PF_6$ gave the corresponding trifluoromethylated esters **96** with excellent yield and enantioselectivity. Screening of various substituents on the aromatic ring such as electron-donating groups (methyl, methoxy) and electron-deficient groups (halogen, phenyl, cyano, trifluoromethyl) gave the corresponding products in moderate to excellent yield (55-91%) with excellent enantioselectivities (84%-96% ee). Notably, the ortho-substituted substrate exhibited slightly lower enantioselectivity (68, 86% ee). Enamide substrates derived from alkyl carboxylic acids and enamides bearing heterocycles, such as pyridine and furan furnished the products with excellent yields and enantioselectivity. Next, a series of alcohols **97** as coupling partners were explored instead

of $(MeO)_4Si$. The simple alcohols such as ethanol, propanol, pentanol, benzyl alcohol, and long-chain alcohols as well as alcohols bearing various functional groups such as cyclopropyl, diol, sulfonyl, alkynyl, etc. resulted in corresponding products **98** with 60-86% yields and 80-97% ee (Scheme 32). Moreover, alcohols bearing heteroarenes including furan and thiophene enamides with chiral alcohols furnished the products with moderate enantioselectivity. Further to showcase the synthetic utility of the products it was successfully converted into optically pure 1,2 diamine using Raney nickel in 90% yield with 99% ee and into antiepileptic drug Levetiracetam

N,N-Dialkylhydrazones are important organic moieties that participate in free radical, pericyclic, and organometallic reactions, as well as they, are valuable organic intermediates. An efficient trifluoromethylation of hetero aromatic aldehyde hydrazones **99** to give trifluoromethylated hydrazones as product **100** using a hypervalent iodine reagent **2** and Cu catalyst was reported by Etienne Pair et al[123] (Scheme 33). To optimize the reaction conditions p-nitrobenzaldehyde N,N-dimethyl hydrazone was considered as a model substrate. Screening results of copper catalysts proved CuCl to be efficient among CuI, CuCl, and chloroform as a better solvent over MeCN, methanol, and dichloromethane when Togni reagent **1** was employed in the reaction. Further, the effect of varying the nature of the dialkyl-amino group of p-nitrobenzaldehyde hydrazones was observed. Various substrates such as 1-piperidinyl, 4-morpholinyl, dibenzyl, diphenyl, and methyl were tested under optimized conditions and hydrazones with the cyclic amino group such as 1-piperidinyl and 4-morpholinyl were found to be effective. To study the substrate scope of the reaction, various (hetero)aromatic N,N-dialkyl hydrazones were employed in the reaction and it was observed that electronic nature of the substituent did not affect the formation of the trifluoromethylated product much. Although higher yields were obtained with electron donating substituents like p-dimethylamino group. Several functional groups such as nitro, cyano, ester, unprotected hydroxyl, and halides including sterically hindered hydrazones and heterocyclic hydrazones such as pyridinyl, pyrazolyl, and furyl endured reaction well. The substrate with two hydrazones gave bistrifluoromethylation in excellent yield.

The utility of the trifluoromethylated products was showcased by transforming the hydrazone group into useful hydrazine using LAH and ketone along with HCl and THF. Synthesis of medicinally important intermediate, trifluoromethylated SAMP hydrazone was demonstrated which was further reduced to hydrazine using LAH.



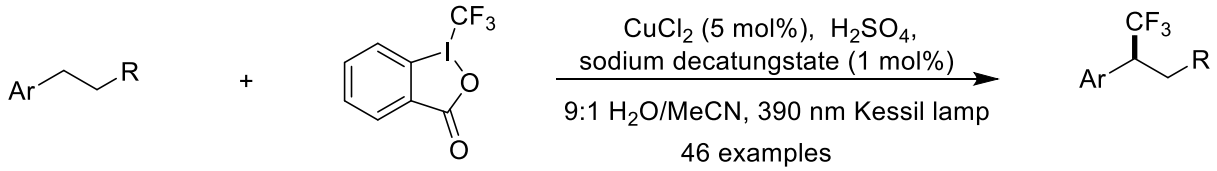
99 **1** **100: 60 - 99%**

R= CH_3, Morpholine; Ar(Het) = 4-Cl-Ph, 4-F-Ph,2-COOMe-Ph, 2-OMe-Ph,4-N,N dimethyl phenyl hydrazone, 4-OH-Ph, 4-N,N diMe-Ph, 2,5 diCl-Ph, 2-Br-Ph, 4- t-Butyl-Ph 3,4,5 trimethoxy-Ph, benzo[d][1,3]dioxole, pyridyl, 1-methyl pyrazole, 2-Nitro furyl

Scheme 33. Cu-catalysed trifluoromethylation of hetero aromatic N,N-dialkyl hydrazones **99** with Togni reagent **1** to trifluoromethylated hydrazones **100.**

The new protocol of trifluoromethylation of non-directed strong aliphatic and benzylic C(Sp^3)–H bond using a combination of decatungstate anion $[W_{10}O_{32}]_4^-$ photochemistry and the copper catalyst was reported for the first time by Sarver et al.[124] Detailed study of reaction mechanism showed that decatungstate anion $[W_{10}O_{32}]_4^-$ gets converted to its photoexcited state. The hydrogen atom is transferred from the distal position of the pyrrolidinium ion to the excited state decatungstate to give alkyl radical and reduced decatungstate. Hypervalent iodine reagent and copper catalyst generate a Cu(II)–CF_3 species which interacts with this alkyl radical to give a corresponding trifluoromethylated product.

For the direct trifluoromethylation of strong aliphatic C–H bonds, different substrates were identified and were successfully converted into desired trifluoromethylated products using Togni reagent **1** (1.25 equiv), sodium decatungstate (1 mol %), a copper(II)chloride precatalyst (5 mol %), an acidic medium (1.2 equiv H_2SO_4), water/acetonitrile (90:10) and a Kessil 40W 390nm lamp as reaction conditions (Scheme 34). Conversion of pyrrolidine to the β-CF_3 product was carried out with 66% yield as a single regioisomer. Using this reaction, conversion of proline to β-CF_3 proline with 58% selectivity, piperidine to γ-CF_3 product 83 % yield and 75% selectivity, azepane to γ-CF_3 product 56% yield and 83% selectivity was achieved. This reaction applies to medicinally important bicyclic systems such as Quinuclidine with 44% yield, Nortropinone with 32% yield, and 7-aza-bicyclo[2.2.1]heptane with 44% yield, and the product formed as a single regioisomer. Electron withdrawing groups such as carboxylic acids, esters, and ketones were effective in improving regioselectivity of the trifluromethylated products with good yields (45–55 %) viz. methyl ester of γ-aminobutyric acid (GABA), an important neurotransmitter, (55% yield, 46% selectivity). Thus, a broad array of cyclic and linear amines were tolerated throughout the reaction. Even various non-amine-bearing compounds were compatible with the reaction. The scope of the reaction was further extended to substrates bearing benzylic C–H bonds as it is an important part of pharmaceutical agents. Various derivatives of phenylethane **101** such as amine, acyl, methyl ester, amide, and chloride well tolerated in this reaction resulting in a trifluoromethyl group at benzylic carbon **102** in good yield (Scheme 34). Benzene ring substituted with electron-withdrawing group such as carbonyl, sulphonamide or electron-donating group such as amine, chloride or sulphonyl group well endured in the reaction with good yield (52-77%). The medicinally important molecules like Nicotine, Sclareolide, Gababutin, Lidocaine, Prilocaine, Celecoxib, and Torsemide were successfully trifluoromethylated with excellent stereoselectivity using this method.



101 **1** **102: 51-77%**

R = H, NH_2, COOMe, CH_2-Cl, Me-CH_2-NH_2, CH_2-OAc
Ar = Ph, 2-Cl-pyridine, pyridine,2-Cl-pyrimidine,
4-sulphonamide-Ph,

Scheme 34. Cu-catalysed trifluoromethylation of benzylic carbon **101** with hypervalent iodine reagent **1** as CF_3 generator.

2.2. Magnesium-Catalysed Trifluoromethylation

Togni and co-workers in 2017 [125,127] reported for the first-time magnesium catalyzed trifluoromethylation of oxindoles substituted at position 3 in presence of the hypervalent iodine reagent, as a source of fluoroalkyl group. The magnesium Lewis acid was selected as a catalyst as it is widely available, cheap, produces non-toxic by-products, and remains active even in compounds containing O and N heteroatoms. On treating oxindole **103** with hypervalent iodine reagent **2** in presence of $MgBr_2$. Et_2O under an inert atmosphere from -78 °C to room temperature for 19 h afforded an excellent yield of trifluoromethylated 3-substituted oxindoles **104** (Scheme 35). It was observed that the yield of the products increased on adding substrate slowly to the reaction mixture in 0.5 h.

103 **2** **104: yield < 99%, *ee* < *87%***

R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $(CH_2)_3CH_3$, $(CH_2)_2OMe$,
CH_2CN, CH_2Ph, CH_2 *p*-FPh, CH_2 Nap
R^1 = H, 5-Cl, 6-Cl, 5-F, 7-F, 5-Br, 5-Me, 5-OMe
R^2 = $CO_2{}^t$Bu, Boc, COOMe, cbz, CO_2iBu, Fmoc, CO_2CH_2Ad

Scheme 35. Mg-catalysed trifluoromethylation of oxindoles **103** using a hypervalent iodine-based CF_3 transfer reagent **2** to enantioenriched trifluoromethylated oxindoles **104.**

Various magnesium salts and Lewis acids such as $MgBr_2$. Et_2O, MgI_2, $MgBr_2$, $Mg(ClO_4)_2$, $Zn(NTf_2)_2$, $Ti(OiPr)_4$, $Cu(OTf)_2$, and $AlCl_3$ were used as the catalyst for the reaction, among which $MgBr_2$. Et_2O was found to be the most effective. On investigating the effect of the N-protecting group on the reaction by using different protecting groups for example acetate, methoxymethyl acetate, and methyl carbamate, it was concluded that the bulky *N*-Boc protecting group is essential and is well endured. The synthesis of oxindole by the given protocol was considered to be well tolerated. Different electron withdrawing and electron donating groups at the C-5, C-6, and C-7 positions of the phenyl ring, as well as short, long, or substituted alkyl chains at the C-3 position of oxindole, provide corresponding products in good yield. Only the presence of a bulky group at the C-3 position resulted in a low yield. Further, the reaction followed radical chain mechanism, proved with the help of TEMPO and styrene, the radical acceptors.

Furthermore, enantioenriched trifluoromethylated oxindoles were synthesized by using $MgBr_2$.EtOH and PyBOX-type ligands along with hypervalent iodine as trifluoromethyl source under above mentioned reaction conditions.[127] Various ligands with aromatic and alkyl substituted at the C-4 position (Figure 6) were screened and it was revealed from the reactions that the aromatic substituents were better than the alkyl substituents to increase enantioselectivity. Ligand **105** with electron donating methoxy group at the C-4 position and ligand **106** provided high enantioselectivity up to 98% and high yield of products.

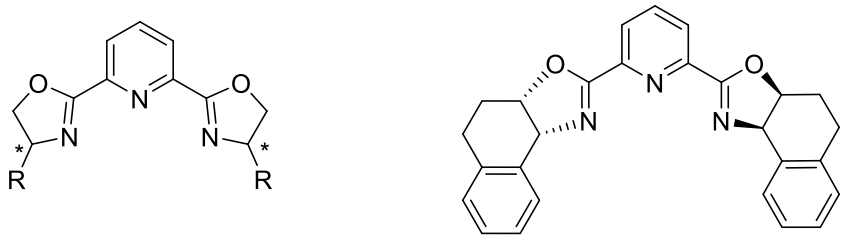
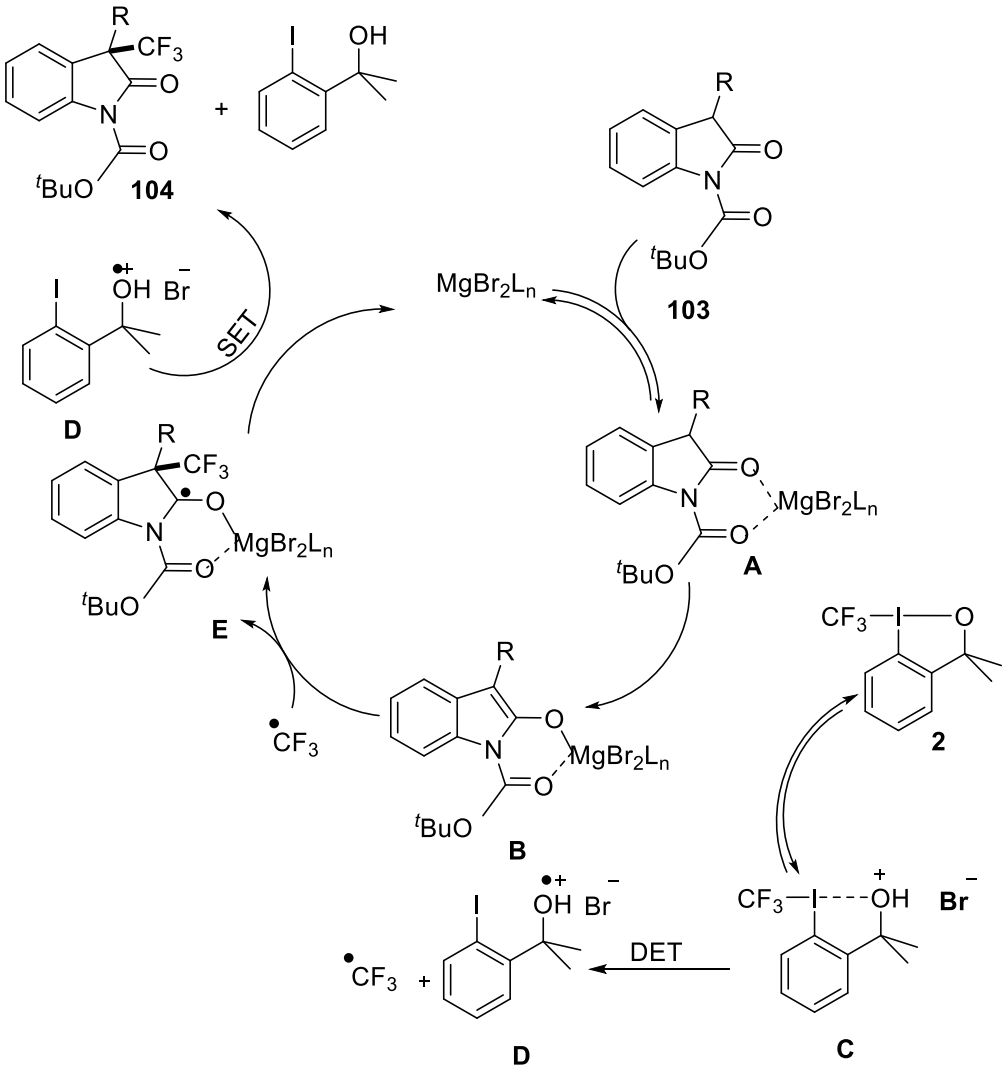


Figure 6. Ligands screened for enantioselective trifluoromethylation of oxindoles.



Scheme 36. Proposed catalytic cycle for magnesium catalysed trifluromethylation.

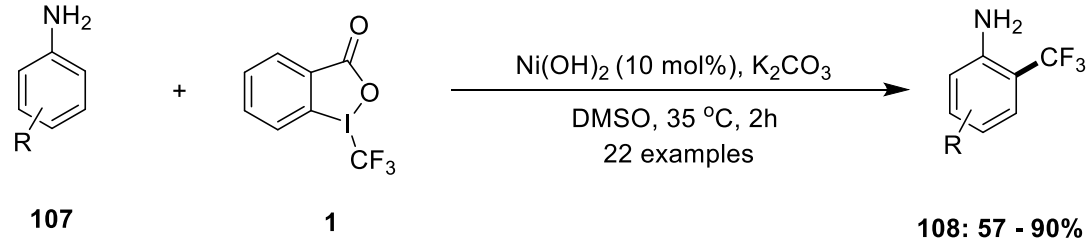
It was observed that using Cbz as N-protecting group afforded highest enantioselectivity upto 98%. Further, no influence of electron withdrawing and electron donating group at C4, C5 and C6 position of oxindole in the reactivity and enantioselectivity was noticed. Various Substituents such as alkyne, nitrile, and alkyl group at C3 position were found to be in good agreement with the reaction whereas the introduction of benzyl group resulted in decrease to 40% ee. The benzyl substituted oxindole gave excellent enantioselectivity

upto 99% and yield upto 97% in presence of Ligand **106** on changing N- protecting group from Cbz to BOC. The trifluoroalkylation reactions in presence of [$MgBr_2$ Ligand **105**] was confirmed to follow radical pathway both experimentally and computational method. It was observed that on adding TEMPO and excess of styrene, the radical scavengers, to the reaction mixture the complete inhibition of reaction occurs confirming radical reaction pathway.

$MgBr_2.Et_2O$ and oxindole coordinate through both the carbonyls present to form complex **A** which combines with hypervalent iodine reagent **2** activated with Lewis acid to produce chelated magnesium-enolate **B** and highly reactive cationic iodonium species **C**. Further, thermally generated internal dissociative electron transfer (DET) generates CF_3 radical and radical cation species **D** from the intermediate **C**.[125,126] Subsequently electrophilic CF_3 radical reacts with intermediate **B** to give radical species **E** which participates in a single electron transfer (SET) with radical cation species **D**, resulting in the formation of trifluoromethylated oxindole **4** along with the regeneration of the catalyst (Scheme 36).

2.3. Nickel-Catalyzed Trifluoromethylation

Trifluoromethylation of free anilines **107** catalyzed by Nickel in presence of a hypervalent iodine reagent **1** as a trifluoromethyl donor dissolved in DMSO at 35 °C was reported in 2018 by Wu and coworkers.[128] Different Nickel sources such as $NiCl_2{\cdot}6H_2O$, $Ni(OTf)_2$, $Ni(PPh_3)_2Cl_2$, $Ni(OAc)_2{\cdot}4H_2O$, $Ni(OH)_2$, $Ni(NO_3)_2{\cdot}6H_2O$, and $NiBr_2$ were tested for the reaction among which $Ni(OH)_2$ gave the best results. The reaction proceeds in presence of a base and thus various bases e.g K_2CO_3, Cs_2CO_3, DMAP, and ^{t}BuOK were scanned and K_2CO_3 was found to be best suited for the high yield of the trifluoromethylated aniline **108**. Among these solvents tested DMSO was the most effective.

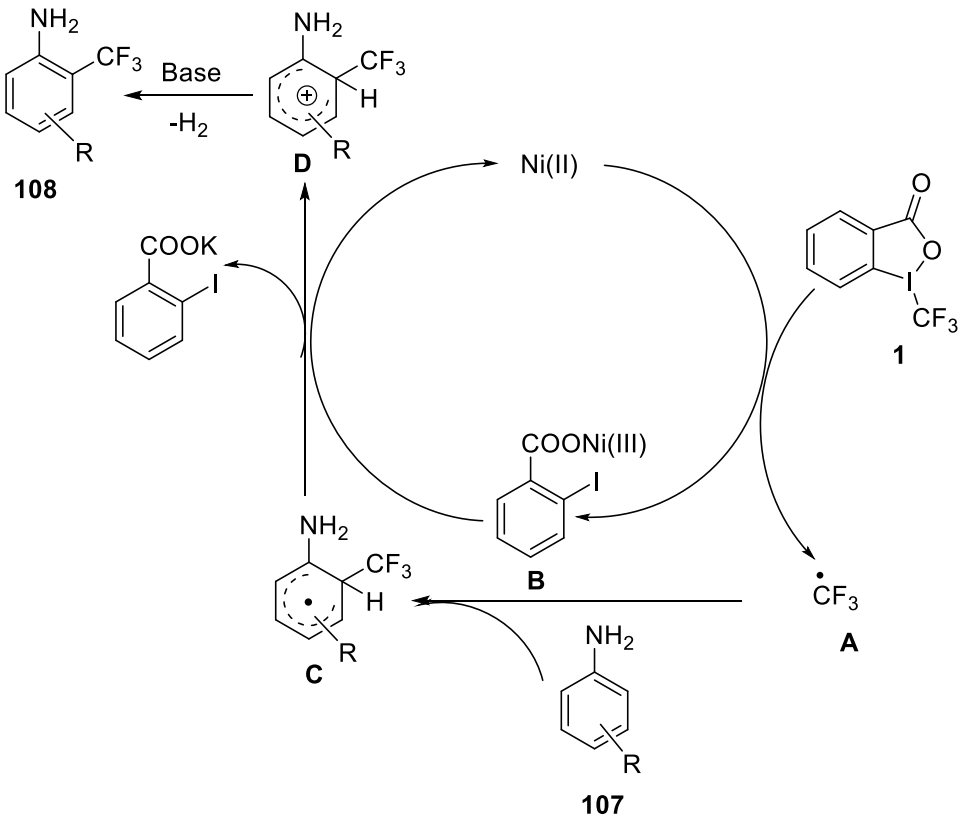


107 **1** **108: 57 - 90%**

R = H, *p*-CH_3, *p*-$CH(CH_3)_2$, *o*-OMe, *m*-OMe, *p*-OMe, *p*-CN, *p*-COOEt, *p*-CF_3, *p*-$COCH_3$, *p*-C_6H_5, $B(OH)_2$, *p*-F, *p*-Cl, *o*-Br, *m*-Br, *p*-Br,

Scheme 37. Ni-catalysed trifluoromethylation of free anilines **107** with hypervalent iodine reagent **1** as CF_3 generator to trifluoromethylated substituted anilines **108**.

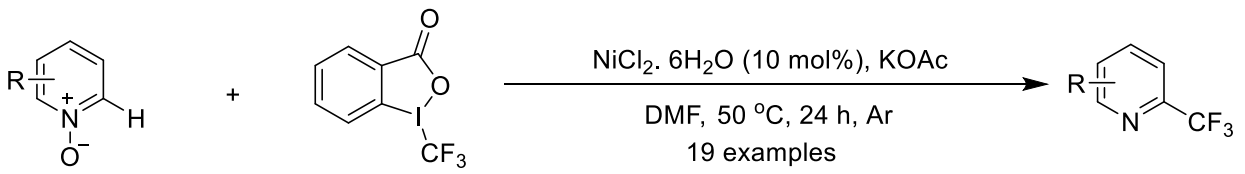
Under the optimized conditions, the reaction completes with diverse free anilines in 2h. Different substituted free anilines **107** were subjected to the reaction and were found to be compatible with the reaction conditions resulting in the corresponding products **108** (Scheme 37). In presence of ortho-substituted free anilines, the mixture of ortho and para trimethylated aniline was obtained as a product. In the case of meta substituted substrate mixture of 3 products was obtained due to the presence of 3 reactive sites. When both the ortho positions are occupied in the substrate the only product obtained was para-CF_3 substituted. The reaction is considered to involve a radical process which was proved by the drastic low yield of the products after adding TEMPO and 1,1 diphenylethylene to the reaction mixture.



Scheme 38. Proposed catalytic cycle for nickel catalysed trifluoromethylation.

The proposed mechanism of the reaction is that the Togni reagent **1** in presence of Ni (II) species generates the CF_3 radical **A** and Ni(III) species **B**. The CF_3 radical attack the ortho position (or para position in case ortho position is occupied) of aniline **107** to afford an intermediate radical **C**. The Ni(III) species **B,** oxidizes intermediate **C** to obtain the carbocation **D** and gives back Ni(II) species to the catalytic cycle. Finally, the deprotonation of **D** gave the desired product **108** in presence of a base (Scheme 38).

In the same year, Wub and co-workers[129] disclosed trifluoromethylation of pyridine N-oxides **109** with hypervalent iodine reagent **1** in presence of Nickel catalyst. A wide range of Nickel catalysts was investigated, and it was discovered that the low-cost $NiCl_2$. $6H_2O$ catalyst was the most effective. Furthermore, a study with various bases revealed that KOAc was the better option in the reaction process. The nickel catalyst and base were quite essential for the reaction as in the absence of Ni catalyst no reaction occurred and in absence of base very low yield of product was obtained. Among different solvents tested DMF suited the reaction most. Thus, the optimum reaction conditions for the synthesis of C-H trifluoromethylated product **110** are 3.0 equiv pyridine N-oxide **109** along with 1.0 equiv Togni reagent **1** in the presence of 10 mol % of $NiCl_2$. $6H_2O$, 3.0 equiv KOAc and DMF as solvents were stirred under an inert atmosphere at 50 °C for 24 h (Scheme 39).



109 **1** **110: 32 - 63%**

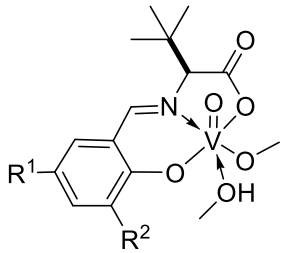
R = *p*-C_6H_5, *m*-C_6H_5, *o*-C_6H_5, *p*-FC_6H_4, *p*-$C_6H_4{}^tBu$,
p-Bn, *p*-$C(CH_3)_3$, *p*-COC_6H_5, *m*-di-Ph

Scheme 39. Ni-catalysed C-H trifluoromethylation of Pyridine N-oxides **109** with Togni reagent **1** to 2- CF_3 Pyridine **110**.

A series of pyridine N-oxides bearing both electron withdrawing and electron donating groups were evaluated and were found to be compatible with the mentioned reaction conditions to yield corresponding Trifluoromethylated pyridine **110**. The ortho and meta substituted pyridine N-oxides in comparison to para substituted were noticed to be less reactive. Under the optimized condition quinoline N-oxides also produced desirable products. To study the mechanism when the trifluoromethylation reaction with p-phenyl pyridine was carried out in optimized conditions the product obtained was in traces. This concludes that the reaction in given conditions requires N-oxide substrate. In the presence of TEMPO, the reaction quenches, and no product was obtained, indicating that the reaction follows a similar radical pathway.

2.4. Vanadyl catalysed Trifluoromethylation

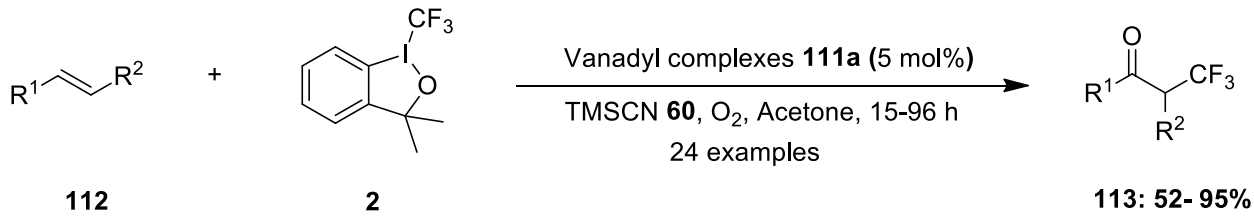
Recently in 2020 Mori et al. [130] demonstrated aerobic 1,2-oxidative trifluoromethylation of styrene, substituted styrene, and monosubstituted alkyl ethenes **112** in presence of a catalytic amount of oxovanadium species at ambient temperature. The corresponding product trifluoromethylated ketones **113** was obtained in good yield (Scheme 40). The six catalysts of $V(O)X_2$ associated with (bi)pyridine, imidazole, and (bis)oxazoline ligands and five different oxovanadium complexes derived from N-salicylidene, tert-leucinate, and salen ligands were examined for the reaction.



111a $R^1 = R^2 = Br$
111b $R^1 = R^2 = {}^tBu$
111c $R^1 = {}^tBu$, $R^2 = Br$

Figure 8. Vanadyl(V) Complexs derived from N-salicylidene type ligand.

Among all bis(oxazoline) bearing vanadyl (IV) triflate and vanadyl-(V) methoxide derived from N-salicylidene **111** (figure 8) were considered best in presence of TMSCN **62** for the high yield of the product.



112 **2** **113: 52- 95%**

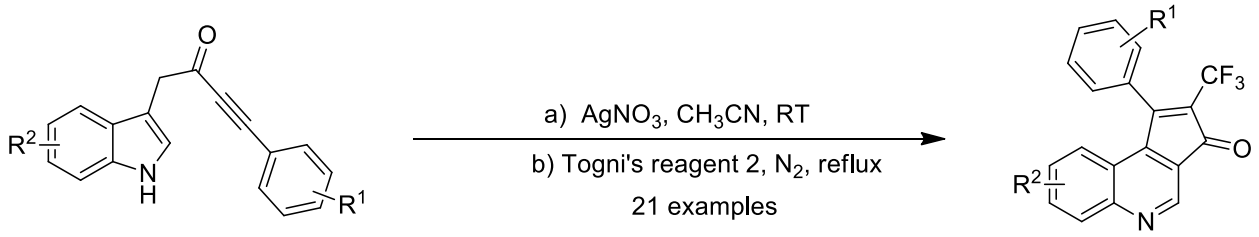
R^1 = H, CH_3; R^2 = C_6H_5, 4-MeC_6H_4, 4-PhC_6H_4, 4-FC_6H_4, 4-$CH_3CO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 3-ClC_6H_4, 3-BrC_6H_4, 3-MeC_6H_4, 2-ClC_6H_4, 1,2 dihydronapthalene, 1H-indene

Scheme 40. Vanadyl- catalysed 1, 2 oxidative trifluoromethylation of olefins **112** using hypervalent iodine reagent **2** to α-trifluoromethylated ketones **113.**

It was observed from the good yield of the products that the new protocol efficiently worked in presence of alkyl, aryl, and electron-withdrawing halo, CF_3, and acetoxy groups at para substituted phenyl system. On the other hand, presence of electron donating p-methoxy group led to no reaction. Similar to para substituted, meta substituted phenyl ring also gave product in good yield whereas ortho substituted phenyl reaction led to the product in low yield. On choosing β substituted styrene as substrate the yield of the product obtained was quite low however on excluding TMSCN **62** from the reaction the yield improved to 56-58%.

2.5. Silver catalysed Trifluoromethylation

Liu and co-workers[131] reported the synthesis of CF_3-containing substituted cyclo pentaquinolinone scaffolds by Ag(I)-catalyzed reaction of substituted indolyl-ynone **114** and hypervalent Iodine reagent. Various silver catalysts such as $AgNO_3$, Ag_2O, Ag_2CO_3, AgOTf, and AgOAc were tested for the reaction. Among all catalysts, $AgNO_3$ was the most efficient in synthesizing the product with a reasonable yield. Furthermore, different solvents, such as 1,2-DCE, CH_3CN, DMSO, THF, and DMF, were explored to boost the yield, with CH_3CN being the best option. Hypervalent iodine reagent was used as the source of CF_3 in the reaction and in its absence spiro-indolenine **116** (Scheme 42) was obtained in quantitative yield. From the results obtained it was considered that spiro-indolenine **116** may be a reaction intermediate and this was proved by reacting it with hypervalent iodine reagent **2**, product **115** in excellent yield was obtained. From all the studies a standard procedure was established in which the substrate indolyl-ynone **114** was allowed to stir with $AgNO_3$ at room temperature for 3 h followed by the addition of hypervalent iodine reagent **2** along with refluxing in an inert atmosphere to afford CF_3-containing cyclopentaquinolinone derivatives **115** in good to excellent yield (Scheme 41).

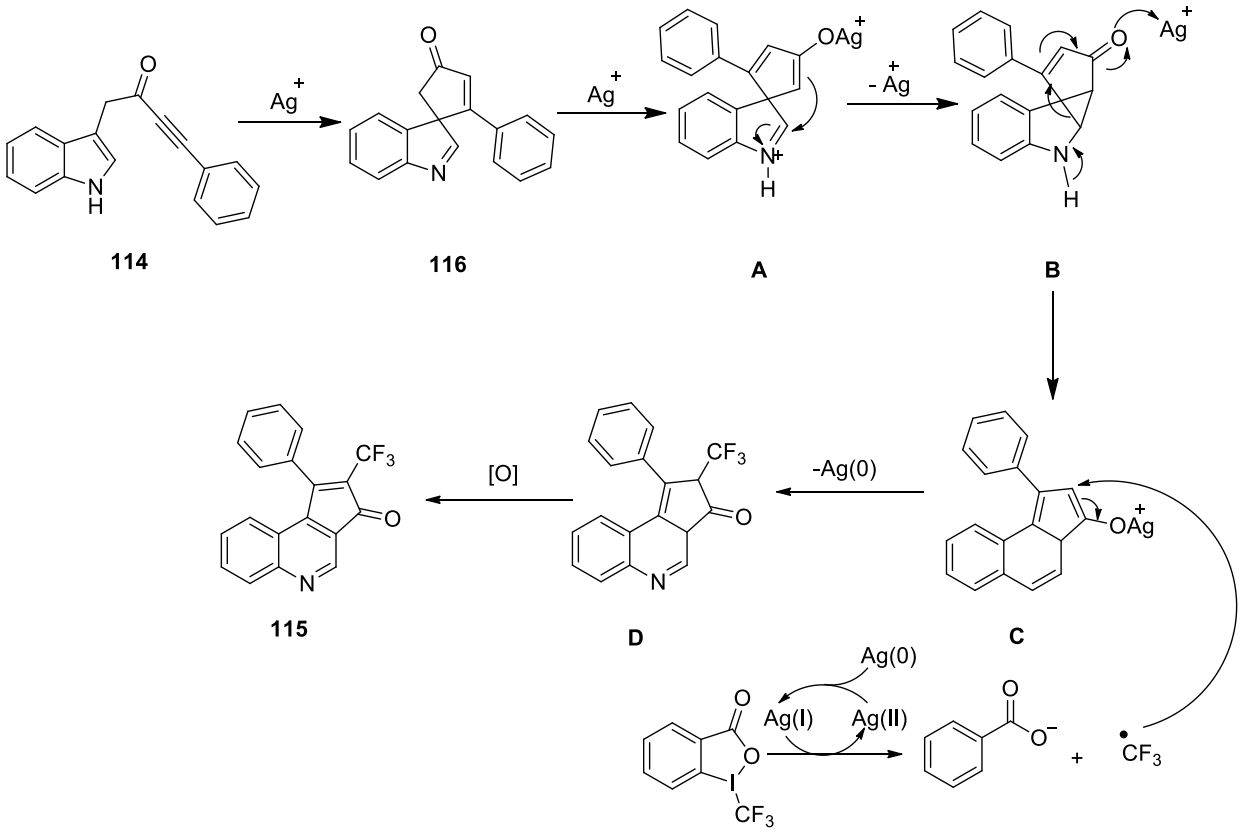


114 **115: 60 - 90%**

R^1 = H, *p*-OMe, *p*-Me, *m*-Me, *p*-F,
p-Cl, *p*-Br, *p*-CF_3, p-Ph$(CH_2)CH_3$
R^2 = H, 5-OMe, 5-Me, 5-F, 5-Cl, 5-Br, 7-Me,

Scheme 41. Ag(I)-catalysed trifluoromethylation of indolyl-ynones **114** with Togni reagent **2** to CF_3 containing cyclopentaquinolinone derivatives **115.**

By using different substituents on the substrate, the scope of the reaction was checked. It was found that the electron withdrawing and electron donating groups on the phenyl ring afforded corresponding quinoline products in good to excellent yield. On replacing the phenyl ring with an alkyl group, the product was formed in traces. The substituents on the indole ring were not sensitive to the reaction and overall, the electron donating and withdrawing groups resulted in the desired product in good to moderate yield. It is important to discuss the low yield of products in the case of substituted 2 phenyl and 4 methyl substituents in the indole ring most probably due to the steric repulsion of neighboring groups.

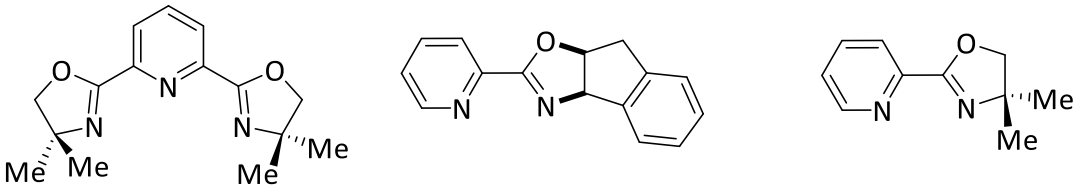


Scheme 42. Proposed catalytic cycle for silver catalysed trifluoromethylation reaction.

According to a plausible reaction mechanism, the Ag(I) acts as a π acid catalyst and activates the triple bond of the substrate to give an intermediate **116** which is formed through dearomatizing spirocyclization. Next, Ag(I) acts as a Lewis acid catalyst, promoting the production of enolate **A** and subsequent cyclopropanation to generate **B**, which is converted into **C**. The CF_3 radical, which is produced from hypervalent iodine reagent when activated by Ag(I), then attack the reactive intermediate **C**, resulting in **D** and Ag (0). Further Ag(0) is oxidized to regenerate Ag(I) and the intermediate **D** is oxidized to yield CF_3 containing quinolone **115** potentially by Ag(II) or Togni reagent 1 (Scheme 42).

2.6. Iron catalysed Trifluoromethylation reaction

Zhu et al.[132] in 2018 reported an iron-catalyzed azidotrifluoromethylation procedure for efficient synthesis of a wide variety of vicinal trifluoromethyl primary amines. The use of a new iron catalyst such as $Fe(NTf_2)_2$, $Fe(OAc)_2$, and $FeCl_2$ with diverse ligands (**L117 – L119**) were studied. In a model reaction allylbenzene **120** in presence of the trifluoromethylating reagent **1**, $TMSN_3$, and $Fe(NTf_2)_2$–**L117** complex afford azidotrifluoromethylated product **121** in good yield which on reduction with Pd/H_2 afford vicinal trifluoromethyl primary amine (Scheme 43).

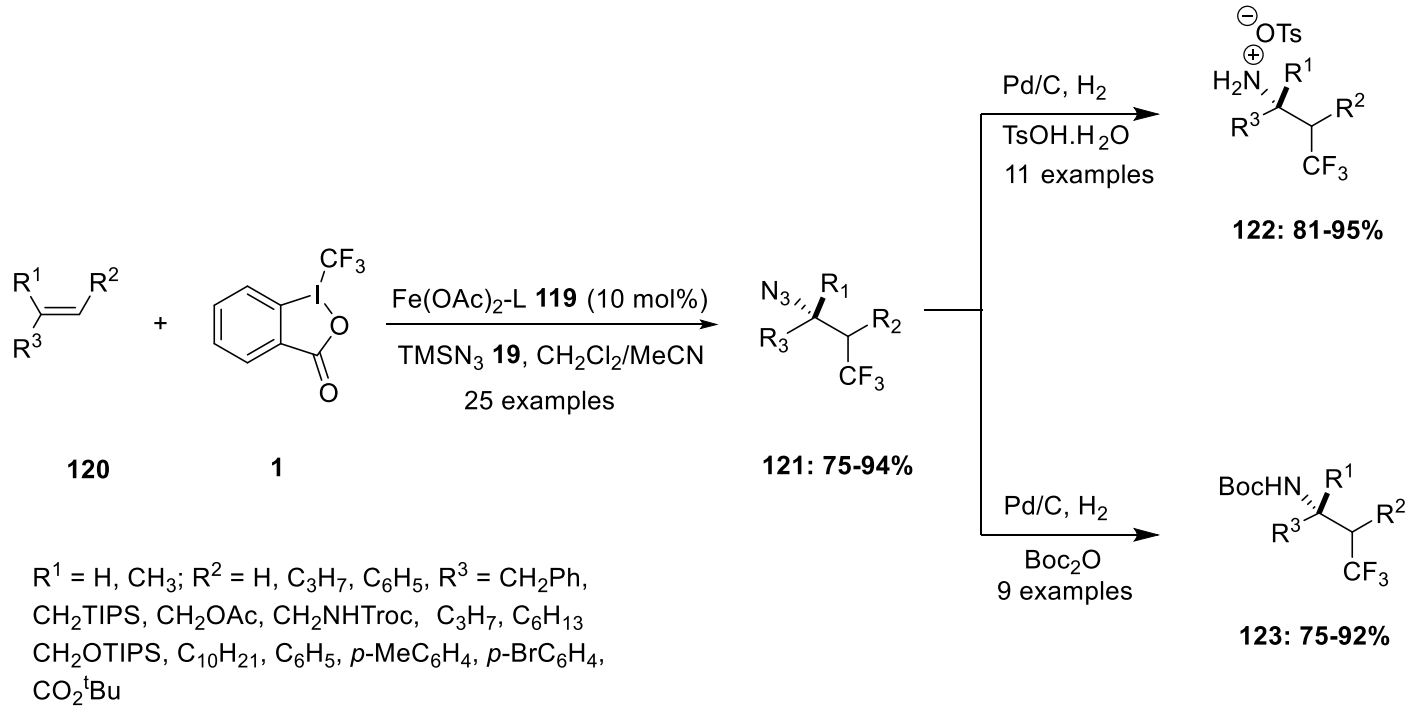


L 117 **L 118** **L 119**

Figure 9. Ligands used in Iron (II)-catalysed azidotrifluoromethylation of Olefines **120.**

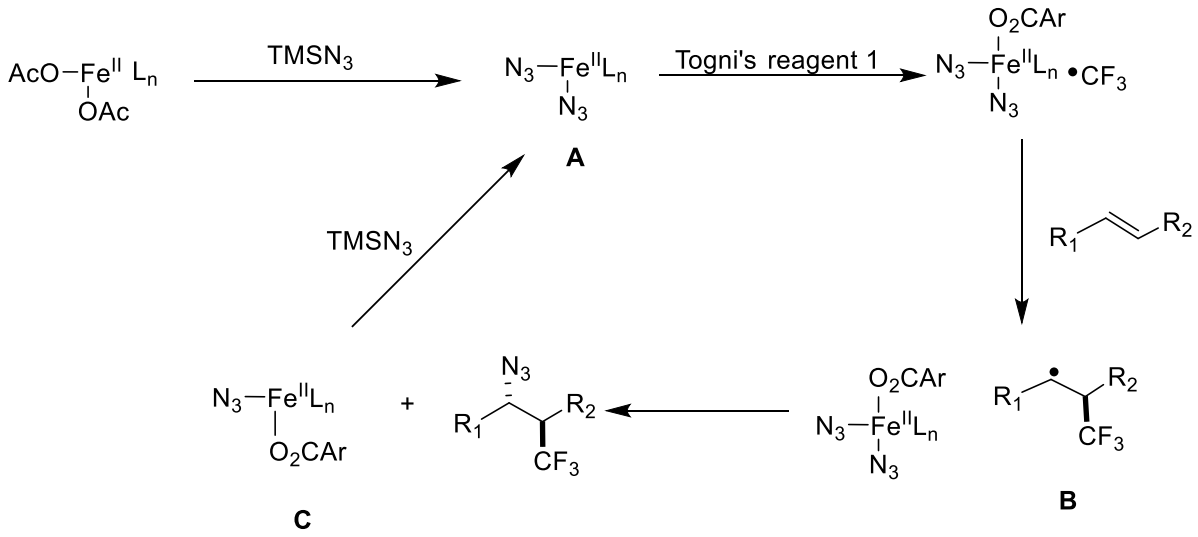
Further on using $Fe(OAc)_2$ with 3 different ligands **L 117, L 118,** and **L 119** it was observed that all three complex yield products but $Fe(OAc)_2$-tridentate **L 117** catalyst was found to be less reactive compared to the $Fe(OAc)_2$-bidentate **L 118** catalyst. Another simpler $Fe(OAc)_2$-bidentate **L 119** complex also catalyzed the reaction and offered excellent results, yielding 86% of the end product in 3 hours. Finally, using a simple reduction–protonation process, azidotrifluoromethylated product **121** was easily transformed to trifluoromethyl aminium salt **122** and **123** (Scheme 43).

A range of olefins and N-heterocycles were explored to determine the scope and limitation of the procedure. Allyl silane, allyl acetate, allyl carbamate, and styrenyl olefins were found to be compatible with this procedure. Mono and di 1,1 disubstituted isolated olefines afforded a good yield of the corresponding products. An aliphatic trans-di-substituted olefin was successfully converted to corresponding trifluoromethylated carbamate. With N-heterocyclic compounds such as indole and pyrrole derivatives as well as different terpenes such as (+)-camphene, and (+)-3-carene, the iron catalyst afforded corresponding trifluoromethylated product. The catalyst was found to be highly tolerant towards different functional groups.



Scheme 43. Iron (II)-catalyzed azidotrifluoromethylation of olefines **120** using Togni reagent **1** as CF_3 radical generator for convenient synthesis of trifluoromethyl amines **122** and **123.**

On evaluating the reactivity of cis- and trans-stilbenes, it was discovered that trans-stilbene was more reactive than its cis-isomer, this suggest that the C–CF_3 bond forming step is not reversible. It was observed that trifluoromethylating reagent **1** was found totally inactive in absence of $Fe(OAc)_2$ catalyst or $TMSN_3$.



Scheme 44. Proposed mechanism for Iron (II) catalysed azidotrifluoromethylation of Olefines.

The proposed reaction mechanism involves activation of $Fe(OAc)_2$–ligand complex in situ by $TMSN_3$ converting it to an iron-azide-derived catalyst **A.** Further, **A** reduce Togni reagent **1** irreversibly via Single Electron Transfer (SET) generating CF_3 radical. The CF_3 radical on addition to an olefin results into a carbo-

radical species **B**, which may be quickly seized by a high-valent iron–azide species through inner-sphere azide-ligand transfer, yielding the desired product **121**. Through the $TMSN_3$-mediated anion metathesis, the ironazide-derived catalyst **A** may therefore be easily reproduced from its precursor **C** (Scheme 44).

3. Conclusions

Owing to the importance of trifluoromethylated products in agrochemicals, and medicinal products; it has become most important to develop such molecules. One of the best choices to carry out trifluoromethylation is Togni reagents which are easy to handle and carry out conversion with maximum efficiency as reported in many cases. This review focuses on metal-catalyzed trifluoromethylation reactions using hypervalent iodine reagents. Details of metal-catalyzed reactions such as Cu, Mg, Ni, Ag, Fe, and V are given here. It was observed in many cases that reaction gave very poor or no yield in absence of the metal catalyst. This emphasizes an undeniable role of metal catalyst in the triflurormethylation reaction. In conclusion, copper catalysts were found to be more compatible with an array of functional groups furnishing better yield and enentioselectivity wherever applicable.Moreover, in many examples an inexpensive and easily available copper catalysts were employed in the reaction and proved to be very much efficient.

It is clear from the reaction mechanisms, described in this review, that the metal catalyst acts as a lewis acid in the reaction and thus facilitates the reaction. As it is observed in the case of iron catalyst, the reaction follows the SET mechanism and CF_3 radical is generated during the reaction which interacts with the reactant. The wide array of reactants were compatible in this reaction ranging from simple alkanes, alkenes, and alkynes to aromatic compounds. Synthesis of versatile building blocks such as trifluoromethylated allenes, carbonyls, ketene aminals, etc. is facilitated using hypervalent Iodine reagent. The introduction of a synthetically useful carbonyl functional group is achieved with efficiency. Moreover, many examples of enantioselective reactions are portrayed in this review. Trifluoromethylation followed by cyclization and or rearrangement furnishing a library of valuable organic molecules is discussed here.

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Authors' Biographies

Revati R. Nagarkar has completed her Masters in Organic chemistry from Department of Chemistry, University of Pune in 2008. Currently, she is working as assistant professor at Modern College of Arts, Science and Commerce, Ganeshkhind, Pune-16, India. Her research interest is mainly in heterocyclic chemistry, green chemistry and sustainable chemistry.

Ritu Mamgain did her Ph.D in Organic Chemistry from the Department of Chemistry, Delhi University, in 2009 under the supervision of Professor. Diwan S. Rawat. After completing her Ph.D, she worked as an Assistant Professor at the DIT Dehradun and later at Graphic Era University Dehradun till 2012. She worked as a Postdoctoral Fellow at the IISER Pune with Prof. Harinath Chakrapani for six months and later joined Modern College Pune as Asst. Professor in 2016. She started working on DST WOS-A research project as a Principal Investigator at the Agharkar Research Institute Pune in 2019. At present, she is continuing her project with Dr Fateh V. Singh at VIT Chennai since November 2021. Her research interests are medicinal chemistry, synthesis of Quinone based ROS generators, design and development of new organic fluorescent molecules as chemical sensors.

Fateh V Singh was born in Ravani Katiry, Bulandshahr, UP, India in 1976. He has completed his MSc in Chemistry from SSV College, Hapur, UP, India in 1998. He has persued his PhD in 2007 with Dr Atul Goel (CSIR-CDRI, Lucknow, India). After the completion of his doctoral studies, he started his first postdoctoral studies (FAPESP fellowship) with Prof. H A Stefani at USP, São Paulo, Brazil and worked with him for more than two years in the area organotrifluoroborate chemistry. In 2010, he joined as Marie Curie postdoctoral fellow with Prof. Thomas Wirth at Cardiff University, UK and worked two years in the area of organoselenium and hypervalent iodine chemistry. He received Dr D S Kothari fellowship in 2013 and worked with Prof. G Mugesh at IISc Bangalore, India for a short stay. In 2014, he started his independent career and joined VIT University, Chennai as an Assistant Professor. Mainly, his research group is interested in the findings of new organoselenium and hypervalent catalysts for organic synthesis. Moreover, his research group is also involved in the development of new organic fluorescent molecules for OLEDs and chemical sensors. Currently, he is having different research grants from Government of India. He has already published more than 55 research papers, several book chapters and review articles.