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Copper(II) Acetate Catalysed Ring-Opening Cross-Coupling of Cyclopropanols with Sulfonyl Azides†

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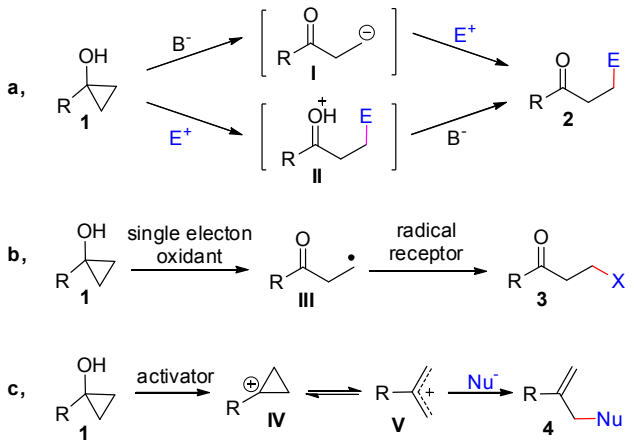
A copper(II) acetate catalyzed ring-opening cross-coupling of cyclopropanol with sulfonyl azide has been developed. By this method, various β-amino ketones have been made efficiently in medium to high yields and venerable functional groups such as benzylic C-H, alkyl and aryl bromides, alkyl sulfonate, silyl ether and alkene are compatible to this reaction conditions. Control experiments have precluded the involvement of both radical and simple copper nitrene intermediates and a possible mechanism featuring key steps of ring-opening metalation and alkyl group migratory insertion into copper nitrene has been proposed.

The energy favouring ring-opening of cyclopropanyl group has been exploited to develop a plethora of elegant synthetic methodologies.[1] Factors that induce the C-C bond breaking in this small ring are extremely diverse depending on the nature of the ring itself, which is defined by substitution pattern on the ring, and reaction conditions. For simple cyclopropanol, the ring opening event normally occurs in a high regioselective fashion due to the effect of hydroxyl group.[2] Roughly, these reactions fall into three categories in the mechanistic respect: a) base and electrophile promoted heterolytic cleavage of cyclopropanol ring through the intermediacy of homoenolate **I** or oxonium ion **II** (Scheme 1, a);[3] b, single electron oxidation induced homolytic breaking of C-C bond resulting in β-carbonyl radical **III** which can be intercepted by various carbon radical receptors (Scheme 1, b);[4] c, activation and removal of the hydroxyl group to give rise to cyclopropanyl cation **IV**, which would open up to form more stable allylic cation **V** for further reactions (Scheme 1, c).[5]



Scheme 1. Three common ring-opening mechanisms of cyclopropanol

The incorporation of a transition metal would expand the reaction scope and improve their usefulness via the intermediary of metal homoenolate **M-I**. Indeed, both palladium and copper are reported to mediate ring-opening coupling reactions of cyclopropanol with carbon-based partners.[6] Very recently, transition metal catalysed conversion of cyclopropanol to β-F, β-CF_3/SCF_3 and β-NR_2 substituted ketones have appeared in literature.[7] On the other hand, sulfonyl azide has been used in various metal catalysed transformations via metal nitrene **M-VI**, metal-nitrene radical **M-VII** or other reactive species as key reaction intermediates.[8] In line with our interests in azide chemistry,[9] we are curious that if the chemistry of cyclopropanol and sulfonyl azide could interwoven through transition metal catalysis (Figure 1).

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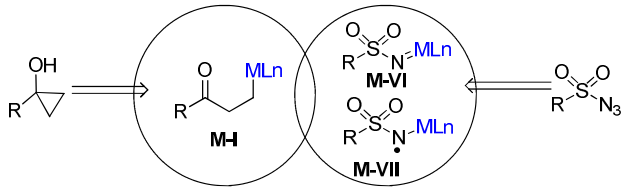
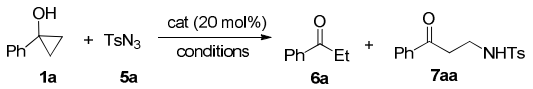


Figure 1. Conceptual depiction of interweaving of cyclopropanol chemistry with sulfonyl azide chemistry by metal catalysis

Our investigation started with catalyst screening for reaction of phenyl cyclopropanol **1a** with tosyl azide **5a** (table 1). In most cases, propiophenone **6a** was the only observable product (see SI-Table 1). To our delight, when a solution of **1a** and **5a** in dichloroethane (DCE) was heated to reflux in the presence of a catalytic amount $Cu(OAc)_2$, ring-opening cross coupling product **7aa** was isolated in 40% yield along with **6a** (table 1, entry 1). Interestingly, while $Cu(acac)_2$ was slightly less effective in terms of yield when DCE was used for reaction media (entry 1 vs 2), $CuBr_2$ was totally ineffective for the cross-coupling reaction (entry 3) indicating the importance of ligand effect. Common Copper (I) complexes all failed to deliver **7aa** (entries 4-6) and only **6a** was obtained. When the reaction was performed in reflux toluene using $Cu(OAc)_2$ as catalyst, the yield of cross-coupling product **7aa** increased to 69% (entry 7). More electron deficient $Cu(hfacac)_2$ showed much poorer activity than $Cu(acac)_2$ in toluene (entry 8 vs 9). Toluene was superior solvent than DCE, THF and chloroform (entries 10-11). Interestingly, in polar solvents such as acetonitrile, DMF and DMSO, **1a** remained intact under the same conditions (entries 12-14).

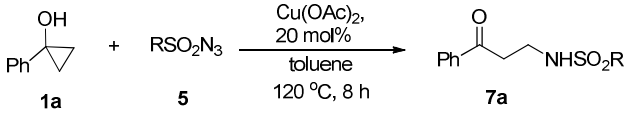
Table 1. Optimization of conditions for Ring opening cross-coupling reaction[a]



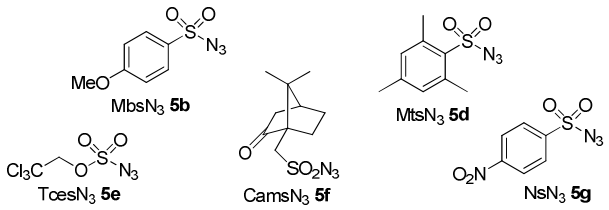
entry	cat	solvent	temp	Products (yield)[b,c]
1	$Cu(OAc)_2$	DCE	reflux	**6a** + **7aa** (40%)
2	$Cu(acac)_2$	DCE	reflux	**6a** + **7aa** (37%)
3	$CuBr_2$	DCE	reflux	**6a** only
4	CuCl	DCE	reflux	**6a** only
5	CuBr	DCE	reflux	**6a** only
6	CuI	DCE	reflux	**6a** only
7	$Cu(OAc)_2$	toluene	reflux	**6a** + **7aa** (69%)
8	$Cu(acac)_2$	toluene	reflux	**6a** + **7aa** (51%)
9	$Cu(hfacac)_2$	toluene	reflux	**6a** + **7aa** (15%)
10	$Cu(OAc)_2$	THF	reflux	**6a** + **7aa** (29%)
11	$Cu(OAc)_2$	$CHCl_3$	reflux	**6a** + **7aa** (27%)
12	$Cu(OAc)_2$	CH_3CN	reflux	No reaction
13	$Cu(OAc)_2$	DMF	120 °C	No reaction
14	$Cu(OAc)_2$	DMSO	120 °C	No reaction

a Conditions **1a** (0.5 mmol), **5a** (0.75 mmol), cat (20% mol%), solvent (2 mL), heating, 12 h; b isolated yields; c yields for **7aa** are reported.

Table 2. Effects of different sulfony azides in the Ring-Opening Cross-Coupling reaction[a]



entry	RSO_2N_3 **5**	product **7a**, yield[b]
1	TsN_3 **5a**	**7aa**, 69%
2	$MbsN_3$ **5b**	**7ab**, 56%
3	MsN_3 **5c**	**7ac**, 61%
4	$MtsN_3$ **5d**	**7ad**, 31%
5	$TcesN_3$ **5e**	**7ae**, 18%
6	$CamsN_3$ **5f**	**7af**, 44%
7	NsN_3 **5g**	-

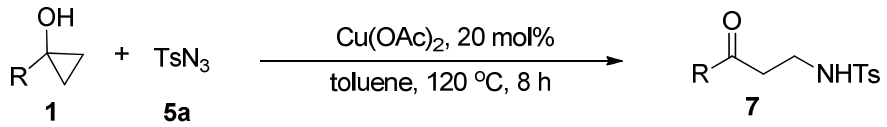


a, conditions, **1a** (0.5 mmol), **5** (0.75 mmol), $Cu(OAc)_2$ (0.1 mmol), toluene (2 mL) in N_2, 120 °C, 8 h; b, isolated yields

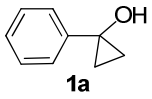
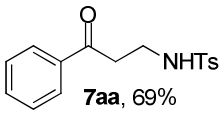
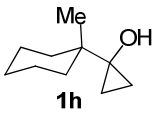
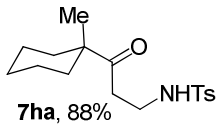
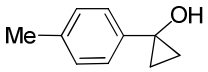
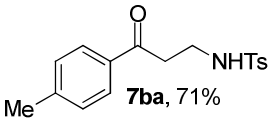
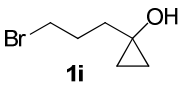
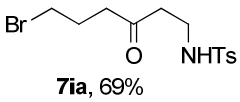
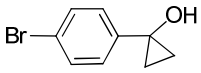
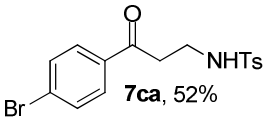
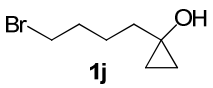
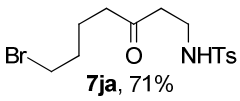
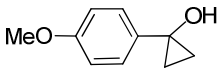
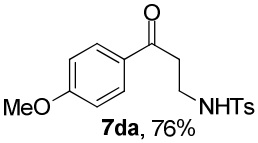
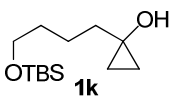
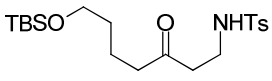
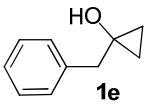
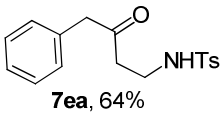
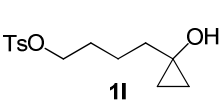
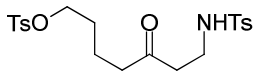
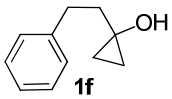
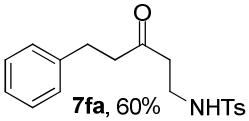
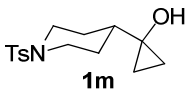
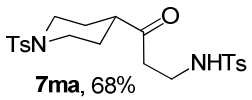
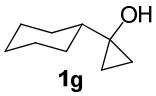
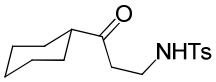
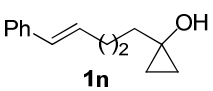
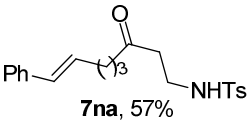
The effect of sulfonyl azide was also checked with $Cu(OAc)_2$ as catalyst and toluene as solvent. TsN_3, $MbsN_3$ and MsN_3 afforded corresponding sulfonyl amides in comparable yields (entries 1-3). $MtsN_3$, $TcesN_3$ and $CamsN_3$ were much inferior reaction partners for this reaction (entries 4-6), and electron deficient NsN_3 reacted with **1a** to give a complex mixture.

Next the scope of cyclopropanol was investigated with TsN_3 as the amination agent (Table 3). For aryl cyclopropanols **1a-1d**, the yield of corresponding β-tosylamidylaryl ketones increased from 52% to 76%, suggesting that the electron-donating group on the phenyl ring favor the ring open/coupling reaction (from entry 3 to 1, 2 and 4). Substrates with benzylic C-H group which is potential reactive site in metal catalyzed reactions involving sulfony azide were also viable for this reaction, as both **7ea** and **7fa** were obtained smoothly (entries 5-6) in comparable yields. 1-Cyclohexylcyclopropanol **1g** reacted with TsN_3 in the same conditions to give **7ga** in an excellent yield (entry 7, 95%). Methyl cyclohexylcyclopropanol **1h** afford **7ha** in 88% yield (entry 8). The slight decrease in yield for **7ha** than for **7ga** might reflect the effect of increased bulkiness at the alkyl group in **1h**. Functional groups such as alkyl/aryl bromide, alkyl silyl ether, alkylsulfonate and alkylsulfonamide were all tolerated in this reaction conditions and related β-tosylamide aryl ketones **7ia-7ma** were all generated in medium to high yields (entries 9-13). It is worth to note that **1n** bearing a vulnerable alkene group was also a good substrate to give **7na** in 57% (entry 14).

Table 3. Substrate scope for cyclopropanol ring-opening cross-coupling reaction[a]

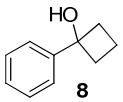


1 5a 7

entry	cyclopropanol **1**	product **7**, yield[b]	entry	cyclopropanol **1**	product **7**, yield[b]
1	 **1a**	 **7aa**, 69%	8	 **1h**	 **7ha**, 88%
2	 **1b**	 **7ba**, 71%	9	 **1i**	 **7ia**, 69%
3	 **1c**	 **7ca**, 52%	10	 **1j**	 **7ja**, 71%
4	 **1d**	 **7da**, 76%	11	 **1k**	 **7ka**, 81%
5	 **1e**	 **7ea**, 64%	12	 **1l**	 **7ka**, 57%
6	 **1f**	 **7fa**, 60%	13	 **1m**	 **7ma**, 68%
7	 **1g**	 **7ga**, 95%	14	 **1n**	 **7na**, 57%

a, conditions, **1a** (0.5 mmol), **5** (0.75 mmol), $Cu(OAc)_2$ (0.1 mmol), toluene (2 mL) in N_2, 120 °C, 8 h; b, isolated yields

Cyclobutanol **8**, cyclopentanol **9** and admantanol **10** failed to undergo analogous ring breaking/coupling reaction when subjected under the same reaction conditions. These experiments underscore the necessity of three-membered ring for the reaction.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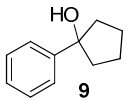
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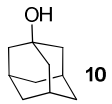
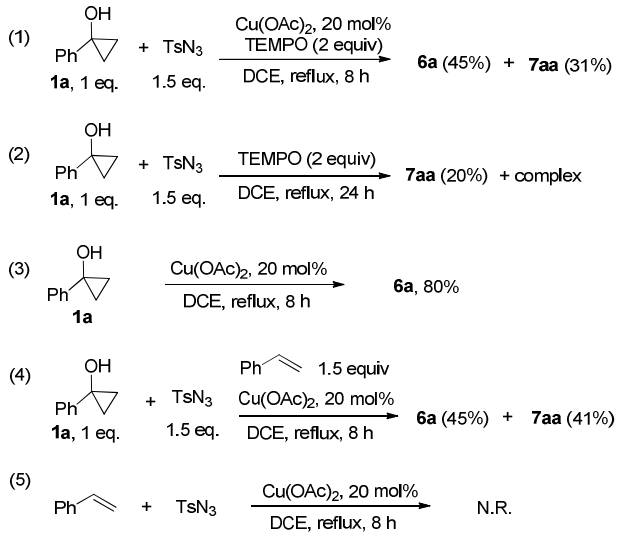

10

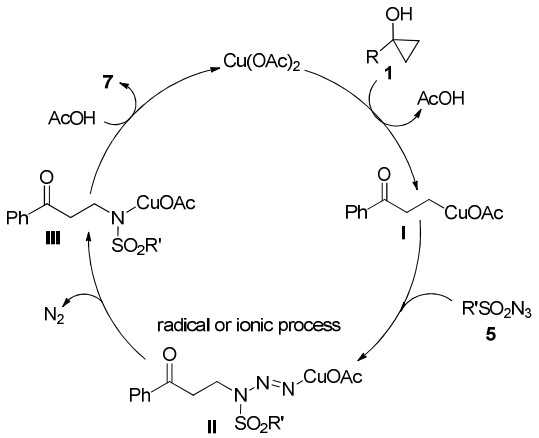
To gain more information about this reaction, control experiments have been carried out (Scheme 2, equations 1-4). It was found that TEMPO has neglectable effect on this

reaction. When a mixture of **1a** (1 equiv), **5a** (1.5 equiv), TEMPO (2 equiv) and $Cu(OAc)_2$ was heated in DCE for 8 hours, **7aa** and **6a** were isolated as sole products (Scheme 2, 1), while increasing the amount of TEMPO to 10 equiv, the formation of **7aa** was not observed. Interestingly, in the prescence of 2 equiv TEMPO but free of $Cu(OAc)_2$, **7aa** could be isolated in 20% yield (Scheme 2, 2). Reaction without sulfonyl azide, phenyl cyclopropanol **1a** was converted to ketone **6a** in a high isolated yield (Scheme 2, 3). In the presence of 1.5 equiv styrene, the reaction took place as normal and no phenyl tosylaziridine was observed (Scheme 2, 4). No reaction happened when styrene and TsN_3 was heated with catalytic amount of $Cu(OAc)_2$ (Scheme 2, 5). These results suggested there was no simple copper nitrene species TsN=Cu(OAc) in the reaction system.[10]

In view our results and literature precedence,[11] a mechanism depicted in scheme 3 was proposed even though a free radical alternate couldn't be excluded at this stage.[12] The catalytic circle starts with a $Cu(OAc)_2$ promoted ring-opening metalation of cyclopropanol **1** to give alkyl copper(II) homoenolate **I**. Protonation of this species would lead to the side product ketone **6**. On the other hand, Cu(II) species **I** could be harnessed by sulfonyl azide 5 either through a transition metal mediated mechanism or a copper coupled radical process to construct the key C-N bond giving rise to intermediate **II** which, upon release of N_2, would produce intermediate **III**. Subsequently, ligand exchange would take place with AcOH to release product **7** and $Cu(OAc)_2$ to complete the catalytic circle. This mechanism is also in line with the ineffectiveness of Cu(I) salts as catalyst for this reaction.



Scheme 2. Several control experiments



Scheme 3. Proposed mechanisms for Ring-Opening Cross-Coupling reaction of Cylopropanol

Conclusions

In summary, we have described a copper(II) acetate catalysed ring-opening cross-coupling of cyclopropanol with sulfonyl azide to produce β-amino ketone. The conditions of this reaction are mild enough to be compatible with a number of fragile functionalities.

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Notes and references

Note

Sulfonyl azides are known explosive compounds and therefore special precautions are paid for their preparation and purification. In some reactions, significant amount of both TsN_3 and $TsNH_2$ were observed after 8 h heating, suggesting that some sulfonyl azides are safe for laboratory use at least in small scale.

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Graphic abstract