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Uracil-Cu(I) catalyst: allylation of cyclopropanols with Morita–Baylis–Hillman alcohols under water-tolerant conditions†

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Inspired by the high affinity of copper with DNA and RNA, a uracil-copper catalytic system was developed to promote ring-opening allylation of cyclopropanols with allylic alcohols under water-tolerant conditions. A new C–OH bond-breaking model can well resolve the trade-off between the need for acidic activators for C(allyl)–OH bond cleavage and the demand for strong basic conditions for generating homoenolates. Therefore, Morita–Baylis–Hillman alcohols, rather than their pre-activated versions, could be incorporated directly into dehydrative cross-coupling with cyclopropanols delivering water as the only by-product. A variety of functionalized δ,ε-unsaturated ketones were obtained in good-to-high yield with high *E*-selectivity.

Introduction

Given that copper has shown a rather high affinity for DNA and RNA,[1] the interaction between copper and thymine/uracil has received great attention.[2] The structure of the uracil/copper complex has been studied by Fridgen[1a] and Lamsabhi[1b] independently, while its catalytic activity has never been explored (Fig. 1). Recently, δ,ε-unsaturated ketones were identified as privileged motifs in various pharmaceutically active natural products[3] and FDA-approved drugs.[4] Since Cha's pioneering reported allylation of cyclopropanol[5] with a stoichiometric amount of Et_2Zn and CuCN·2LiCl (Fig. 1a), allylation of low-cost metal homoenolates was considered as the state of the art to access δ,ε-unsaturated ketones.[6] Yin,[7a] Trost,[7b] and Sawamura[7c] have also paid an extensive amount of attention to addressing the asymmetric versions of related copper catalysts (Fig. 1a). The catalytic activity of other low-cost transition metals (Co and Ni) was also explored by Yoshikai and co-workers.[8] Despite these impressive achievements, equivalents of a strong base and cryogenic and/or anhydrous conditions are generally inevitable for guaranteeing the generation of metal homoenolates.[5–7] In addition, only activated allylic precursors[5–8] were compatible for the concomitant allylation. In terms of economic and ecological concerns, the direct incorporation of the most abundant allylic alcohols[9] into ring-opening allylation is highly desirable, especially in pharmaceutical industries as water will be the only by-product.[10] However, the irreconcilable

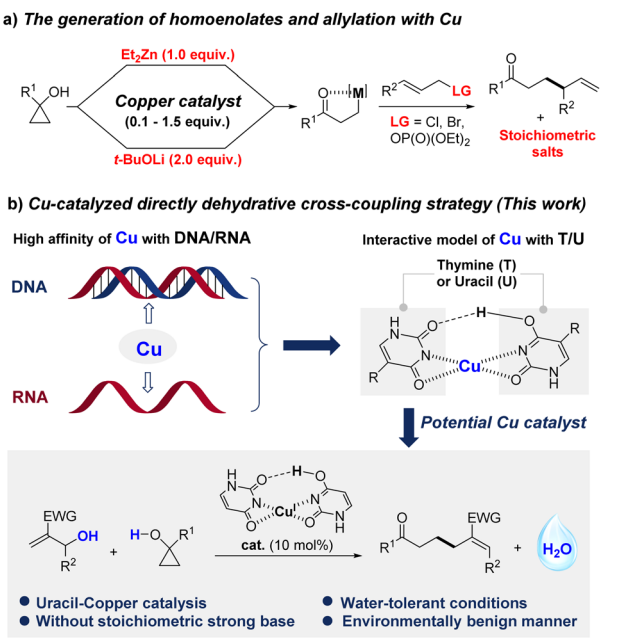

Fig. 1 Copper-promoted allylation of cyclopropanol *via* homoenolates.

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contradiction between the acidity activator for C(allyl)–OH bond cleavage[11] and strong basic environmental[5–8] requirements for generating homoenolates has challenged the development of the catalyst. In our continuing green chemistry efforts, we paid special attention to C–OH bond cleavage[12] and related transformations. As one of the most versatile building blocks, Morita–Baylis–Hillman (MBH) alcohols have garnered widespread attention in organic synthesis,[13] and seen growing interest in the field of medicine.[14] We herein report a uracil-Cu catalytic system for the ring-opening allylation of cyclopropanols with MBH alcohols in a dehydrative cross-coupling manner, which affords water as the only by-product (Fig. 1b).

Results and discussion

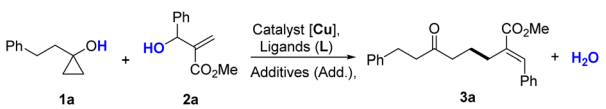
At the onset of our study, we initially evaluated the dehydrative coupling potential of 1-phenethylcyclopropan-1-ol (**1a**) with methyl 2-(hydroxy(phenyl)methyl)acrylate (**2a**) using a copper catalytic system. Notably, although MBH adducts (*tert*-butyl carbonates) are recognized as versatile building blocks in various fields, the allylation of cyclopropanols suffered from poor stereoselectivity or other competitive processes.[15]

After carefully evaluating copper precursors (see Supporting Information (ESI) for details†), we found that $Cu(MeCN)_4PF_6$ provided the best results, yielding the desired **3a** in 25% yield (Table 1, entry 4). Replacement of $Cu(MeCN)_4PF_6$ with CuBr (Table 1, entry 1), $Cu(OAc)_2$ (Table 1, entry 2), or $Cu(MeCN)_4BF_4$ (Table 1, entry 3) under the same reaction conditions resulted in either trace amounts or no reaction at all. With subsequent screening of solvents and altering the ratio of **1a**/**2a**, DMF improved the yield of **3a** to 41% (Table 1, entry 5). The use of common ligands, such as 1,10-phenanthroline or 4,4′-bipyridine, had a negligible impact on the yield of **3a** or even proved detrimental (Table 1, entries 6 and 7). Then, we selected uracil as the ligand to combine with $Cu(MeCN)_4PF_6$, and to our delight, the yield of **3a** improved to 65% (Table 1, entry 8). In sharp contrast to the previously reported catalytic system, which was sensitive to moisture, water played an essential role in this transformation. With the assistance of 4.0 equivalents of water, the yield of **3a** improved to 72% (Table 1, entry 9). This result indicated that our developed reaction was fully water-tolerant. After carefully evaluating all reaction parameters, we found that the addition of 7 mol% of Me_2NH actively stabilized the yield and improved the reproducibility (Table 1, entries 10 and 11). When uracil was replaced by thymine, a slightly lower yield of **3a** was obtained (Table 1, entry 12). However, only a trace amount of **3a** was detected when cytosine rather than uracil was introduced into this reaction (Table 1, entry 13). These results revealed that the combination of uracil/thymine with copper was crucial for promoting the desired transformation. In addition, the reaction also proceeded smoothly even at a lower temperature (40 °C), albeit delivering **3a** in a moderate yield (Table S1, entry 14†). Upon decreasing the catalyst loading to 5 mol%, **3a** could also be obtained in a 45% yield (Table 1, entry 15).

To assess the reproducibility of this transformation, we followed the methodology reported by Glorius *et al.*[16] The parameters including concentration, levels of water and oxygen, scales, and temperature only have a limited effect on the transformation, indicating that this strategy has a good reproducibility (Fig. 2).

Next, we explored the generality of the reaction with Morita–Baylis–Hillman (MBH) alcohols under optimized conditions. As shown in Table 2, various MBH alcohols were successfully incorporated into the dehydrative cross-coupling with cyclopropanols, delivering corresponding products **3a–3ab** in high yield. The electronic property (**3b–3i**) and position (**3j–3s**) of the substituent on the phenyl ring had limited effect on the yield. Even strong electron-donating (**3b**) or electron-withdrawing (**3h**,

Table 1 Optimization of the reaction conditions[a]



Entry	[Cu] (10 mol%)	[L] (20 mol%)	Add.	3a (%)[b]
1[c]	CuBr	—	—	<5
2[c]	$Cu(OAc)_2$	—	—	n.r.
3[c]	$Cu(MeCN)_4BF_4$	—	—	5
4[c]	$Cu(MeCN)_4PF_6$	—	—	25
5	$Cu(MeCN)_4PF_6$	—	—	41
6	$Cu(MeCN)_4PF_6$	1,10-Phen.	—	25
7	$Cu(MeCN)_4PF_6$	Bipyridine	—	32
8	$Cu(MeCN)_4PF_6$	Uracil	—	65
9	$Cu(MeCN)_4PF_6$	Uracil	H_2O	72
10[d]	$Cu(MeCN)_4PF_6$	Uracil	H_2O	80
11[d]	$Cu(MeCN)_4PF_6$	Uracil	H_2O and Me_2NH	82 (80)
12[d]	$Cu(MeCN)_4PF_6$	Thymine	H_2O and Me_2NH	70
13[d]	$Cu(MeCN)_4PF_6$	Cytosine	H_2O and Me_2NH	<5
14[d,e]	$Cu(MeCN)_4PF_6$	Uracil	H_2O and Me_2NH	46
15[d,f]	$Cu(MeCN)_4PF_6$	Uracil	H_2O and Me_2NH	45

[a] Experimental conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), Cu (catalyst) (0.02 mmol), L (ligands) (0.04 mmol) and Add. (for entries 9–15, 4.0 equiv. of H_2O was added and 7 mol% of Me_2NH was also added for entries 11–15) were mixed in DMF (2.0 mL) at 60 °C (metal bath). [b] Determined by ^1H NMR of the crude product with mesitylene as the internal standard. In parentheses are isolated yields. [c] **1a** (0.2 mmol) and **2a** (0.24 mmol) were mixed in THF (2.0 mL). [d] **1a** (0.4 mmol) and **2a** (0.2 mmol). [e] At 40 °C (metal bath). [f] $Cu(CH_3CN)_4PF_6$ (0.01 mmol) and uracil (0.02 mmol) were used. In all the tested cases, the ratio of *E*/*Z* is over 99/1.

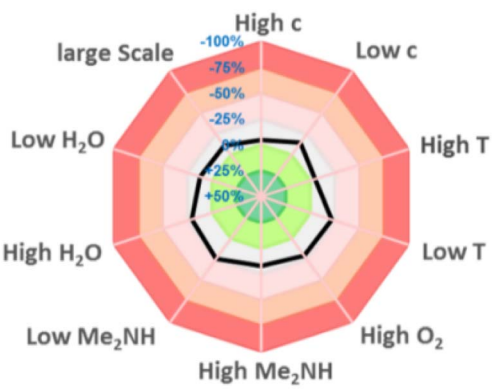
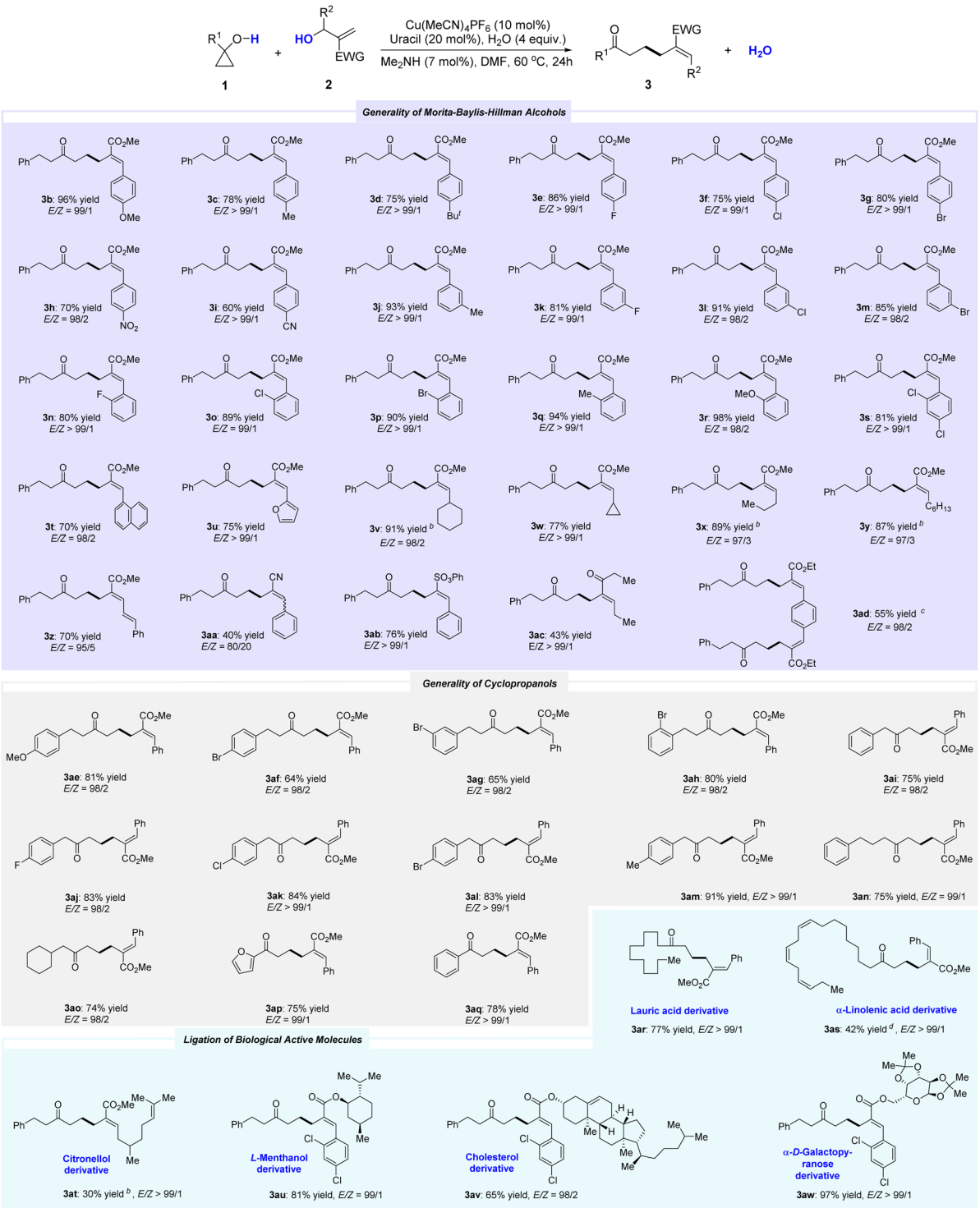


Fig. 2 Sensitivity assessment.

Table 2 Dehydrative cross-coupling between cyclopropanols and allylic alcohols[a]



[a] Experimental conditions: **1** (0.4 mmol), **2** (0.2 mmol), $Cu(MeCN)_4PF_6$ (0.02 mmol), uracil (0.04 mmol), H_2O (0.8 mmol), and Me_2NH (2.4 μL, 0.014 mmol) were mixed in DMF (2.0 mL) at 60 °C (metal bath) for 24 h. [b] $Cu(MeCN)_4PF_6$ (0.03 mmol), uracil (0.06 mmol). [c] **1a** (0.8 mmol), **2** (0.2 mmol), $Cu(MeCN)_4PF_6$ (0.04 mmol), uracil (0.08 mmol), Me_2NH (4.8 μL, 0.028 mmol) and H_2O (1.6 mmol). [d] $Cu(MeCN)_4PF_6$ (0.04 mmol), uracil (0.08 mmol).

3i) groups were tolerated well. Phenyl rings bearing *o*-substituents and poly-substituents also afforded corresponding products (**3n–3s**) in high yield. MBH alcohols with fused rings (**3t**) and hetero-aryl moiety (**3u**) were also amenable to this reaction. Besides aryl-substituted MBH alcohols, alkyl-substituted versions also worked well (**3v–3y**). MBH alcohols bearing cyclic

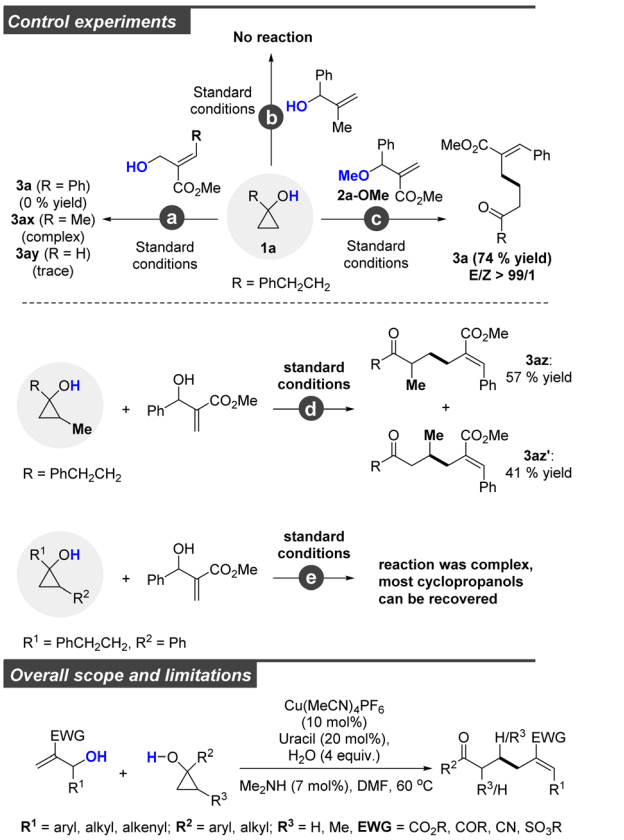
(**3v**, **3w**) or acyclic (**3x**, **3y**) alkyls could also participate in this protocol, delivering the desired products in high yields. In addition, although the yield was slightly lower, methyl (*E*)-6-oxo-8-phenyl-2-((*E*)-3-phenylallylidene)octanoate (**3z**) can be obtained by selecting methyl (*E*)-3-hydroxy-2-methylene-5-phenylpent-4-enoate. 2-(Hydroxy(phenyl)methyl)acrylonitrile was identified as a suitable precursor for this reaction, although it was only 80/20. MBH alcohols derived from phenyl ethenesulfonate (**3ab**) or ketones (**3ac**) were proven to be viable coupling partners for this reaction, even carbonyl groups with adjacent acidic C–H bonds.

By using ethyl 3-(4-(2-(ethoxycarbonyl)-1-hydroxyallyl) phenyl)-2-hydroxybut-3-enoate, the double dehydrative coupling version can also proceed well, albeit affording **3ad** in slightly lower yield.

Subsequently, the generality of cyclopropanols was explored. A variety of cyclopropanols were found to readily react with MBH alcohols. For 1-phenethylcyclopropan-1-ol derivatives, the position of the substituent (*ortho*, *para*, or *meta*) had little effect on the overall transformations (**3ae–3ah**). Even 1-benzylcyclopropan-1-ol was a competent coupling partner, regardless of the electron-withdrawing (**3aj–3al**) or electron-donating (**3am**) groups on the phenyl rings. The reaction with 1-(3-phenylpropyl)cyclopropan-1-ol also proceeded smoothly to deliver **3an** in 75% yield. Moreover, selecting 1-(cyclohexylmethyl)cyclopropan-1-ol as the feedstock allowed for the high-yield synthesis of methyl (*E*)-2-benzylidene-7-cyclohexyl-6-oxoheptanoate (**3ao**). In addition to 1-alkyl-substituted cyclopropanol, both 1-phenyl- and 1-furan-2-yl-substituted versions were also found to participate in this transformation, affording **3ap** and **3aq** in high yields, respectively. The structure and configuration of the double bond in **3aq** (CCDC: 2202510) were determined by X-ray analysis.

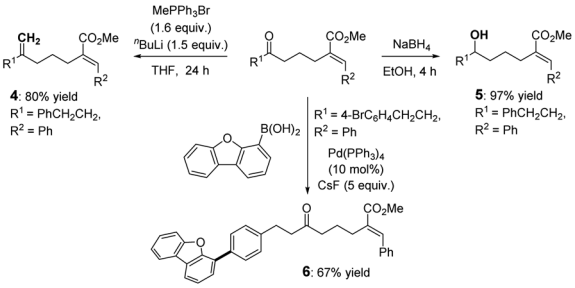
We aimed to demonstrate the versatility of this synthetic method by applying it to several biologically active compounds. As shown in Table 2, the cyclopropanol derived from lauric acid was smoothly converted to the desired product **3ar** in high yield. The skeleton of alpha-linolenic acid was also incorporated into the product (**3as**) in moderate yield while maintaining the *Z*-configuration of the double bond. Moreover, all the MBH alcohol precursors bearing the motifs of citronellol, *L*-menthanol, cholesterol, and alpha-D-galactopyranose could be smoothly transformed, producing corresponding **3at–3aw** effectively. These results opened up possibilities for the potential utility of this protocol in pharmaceutical-related studies.

Having demonstrated the versatility of this transformation concerning biologically active molecules, we attempted to gain more insights into the reaction mechanism by conducting some related control experiments (Scheme 1, top). Under identical conditions, no corresponding product was detected when the allylic alcohol was replaced by its isomer (reaction a). These results indicated that a copper-catalyzed allylic S_N2' process was involved in this transformation, and steric hindrance at the γ-position of allylic alcohols was disfavored. In addition, only a trace amount of **3ay** was detected when ethyl 2-(hydroxymethyl)acrylate was selected as the coupling partner. This is because ethyl 2-(hydroxymethyl)acrylate favored self-



Scheme 1 Control experiments and overall scope and limitations.

polymerization. Similarly, 2-methyl-1-phenylprop-2-en-1-ol could not be consumed under standard conditions (reaction b), which implied that the electron-deficient double bond was essential for this reaction. In contrast, a comparable yield of **3a** was obtained when the hydroxyl group was protected (**2a-OMe**) (reaction c). Moreover, we conducted experiments to explore the cyclopropane ring with substitutions at the distal carbons present at the C–OH positions. As is depicted, the C–C bond cleavage has poor selectivity, with the desired **3az** and **3az′** obtained in good yields (**3ax**/**3ax′** = 57/41) (reaction d). When a sterically demanding substance (R = CH_2CH_2Ph or Ph) was selected, the reaction was sluggish with most cyclopropanols being recovered and only a trace amount of the desired product was detected. These results revealed that the ring opening of



Scheme 2 Preliminary protocol applications.

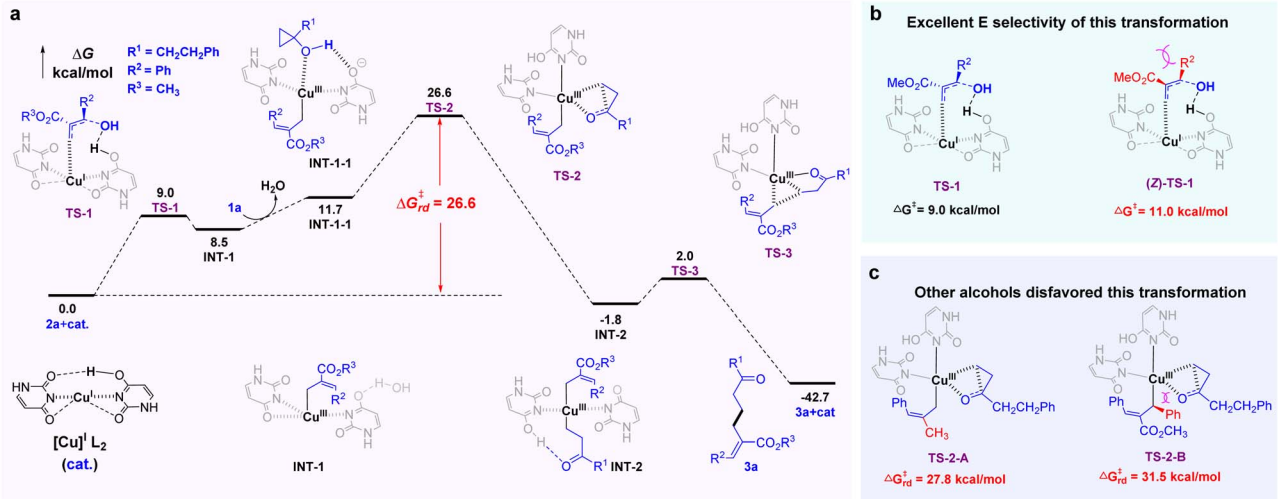


Fig. 3 Mechanism investigation with the assistance of DFT calculation.

cyclopropanol has poor selectivity, and the steric effect on the copper homoenolates at either α- or β-position of the carbonyl group disfavoured the following cross-coupling process. Therefore, this method appears to be primarily limited to monosubstituted cyclopropanols. To clearly outline the overall scope and limitations, we incorporate structure restriction at the bottom of Scheme 1.

The utilization of these products was preliminarily demonstrated by related derivation reactions (Scheme 2) *via* Wittig reaction (**4**), reduction (**5**), and Suzuki-coupling (**6**) reactions.

The mechanism and energetic parameters of the reaction were investigated by DFT calculations at the B3LYP+D3(BJ)/def2TZVPP//B3LYP/def2svp level (Fig. 3; see ESI for computational details†). The optimized original Cu(I) catalyst[17] tends to adopt a two-coordinate linear geometry. In the first step, the C–OH bond activation of **2a** and addition of the terminal olefinic carbon onto copper occur in a concerted manner *via* transition state **TS-1**, delivering Cu(III)-allyl intermediate **INT-1**. Then, reactant **1a** enters the ligand field of Cu(III)[17] to form the precursor complex **INT-1-1**. The C–C bond activation of the cyclopropane ring is required to overcome a high-lying transition state **TS-2**, which delivers Cu(III) complex **INT-2** with two Cu–C coordinate bonds. Finally, C–C reductive elimination *via* transition state **TS-3** gives the desired product **3a** with regeneration of the original Cu(I) catalyst. According to the calculated energy profiles, the rate-determining free-energy barrier of the reaction is 26.6 kcal mol^{-1}, the difference between **TS-2** and the initial point, which is consistent with the experimental temperature of 60 °C (Fig. 3a). Moreover, the high *E*-selectivity of this transformation can be attributed to the steric effects, which result in the high energy of (*Z*)-**TS-1** (Fig. 3b). The higher energy of the rate-determining free-energy barrier (Fig. 3c) can account for the main reasons as to why some allylic alcohols cannot be consumed in the transformation (**TS-2-A** and **TS-2-B**). Although **TS-2-A** (27.8 kcal mol^{-1}) is only 1.2 kcal mol^{-1} higher than **TS-2** (26.6 kcal mol^{-1}), the destabilization of **TS-2-A** might make the overall reaction difficult in the absence of EWG. This is because the present activation-free energy of 26.6 kcal mol^{-1} is close to the upper limit of the allowed value at 333.15 K, and an additional increase in activation free energy would prevent an efficient reaction (for details, see ESI†).

Conclusions

In summary, we have developed a direct dehydrative cross-coupling protocol by selecting readily available MBH alcohols with cyclopropanols, which produce water as the only by-product. The Cu-uracil catalytic system has resolved the trade-off between the need for acidic activators for C(allyl)–OH bond cleavage and the demand for strong basic conditions for generating homoenolates. The protocol has demonstrated a broad substrate scope, delivering δ,ε-unsaturated ketones in high yields with exceptional stereoselectivity. Significantly, the usefulness of the methodology has been demonstrated by incorporating biologically active molecules. This study has also opened up possibilities for other metal-uracil catalytic processes for dehydrative allylation, although only MBH alcohols have been investigated thus far.

Data availability

All of the necessary data have been included in the ESI.†

Author contributions

J. H. performed the laboratory experiments (optimization, substrate scope, application, and mechanistic studies) and analyzed the experimental data. X. L. performed the laboratory experiments for substrate scope. K. Y. performed the laboratory experiments for mechanistic studies. L. Z. conducted the DFT calculations. T.-P. L. directed the investigations and prepared the manuscript. P. X. conceived and directed the investigations, analyzed the experimental data, and prepared the manuscript. All authors interpreted the results and contributed to the development of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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