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Olefin-Supported Cationic Copper Catalysts for Photochemical Synthesis of Structurally Complex Cyclobutanes

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Abstract: The sole method available for the photocycloaddition of unconjugated aliphatic alkenes is the Cu-catalyzed Salomon–Kochi reaction. The [Cu(OTf)]₂•benzene catalyst that has been standard in this reaction for many decades, however, is air-sensitive, prone to photodecomposition, and is poorly reactive towards sterically bulky alkene substrates. Using bench-stable precursors, we have designed an improved catalyst system with superior reactivity and photostability that offers significantly expanded substrate scope. The utility of this new catalyst for the preparation of sterically crowded cyclobutane structures is highlighted through the preparation of the cores of the natural products sulcatine G and perforatol.

Cyclobutane rings feature in more than 2600 known natural products,¹ and the challenge of synthesizing these compounds has motivated the development of photochemical cycloaddition reactions for many decades. Numerous mechanistically distinct strategies for [2+2] photocycloadditions are known.² The most well-developed of these involve: (1) direct photoexcitation of olefinic compounds featuring optical transitions in the visible or near-UV range;³ (2) triplet photosensitization of substrates with triplet state energies sufficiently low enough to enable Dexter energy transfer;⁴ and (3) photoredox reactions of alkene radical ions generated via photoinduced electron transfer.⁵ Notably, each of these activation modes requires the use of alkene substrates with extended π conjugation. Unconjugated aliphatic alkenes generally have short-wavelength optical transitions (<200 nm)^{2a} that are not accessible with commercial UV photoreactors. They also feature higher-energy triplet excited states (76-84 kcal/mol)⁶ and electrochemical potentials⁷ that lie outside of the range of most common photoredox catalysts.⁸ The sole method suitable for the [2+2] photocycloaddition of aliphatic alkenes is the Cu(OTf)-catalyzed process originally reported by Kochi and Salomon in 1973.^{9,10} The key intermediate in this reaction is a 2:1 alkene-copper complex that absorbs at wavelengths that are easily accessible using standard benchtop UV reactors (ca. 270 nm). This absorbance corresponds to a metal-to-ligand charge transfer (MLCT) transition,¹¹ which initiates an inner-sphere bondforming cascade that can convert simple aliphatic alkenes into cyclobutanes that are simply not accessible using direct, sensitized, or electron-transfer photochemistry (Figure 1A).

Although the Salomon–Kochi photocycloaddition has featured in several total syntheses (Figure 1B),¹² the conditions for this reaction have not been significantly reinvestigated since its early reports, and the utility of this method has been hampered by its narrow scope. Successful cycloaddition requires the

formation of a copper bis(alkene) complex that is relatively unstable, and a variety of common substrate structural features



Figure 1: a) Salomon–Kochi reaction and catalyst limitations b) Total synthesis application of Salomon–Kochi reaction c) Sterically challenging target natural products d) Newly developed catalyst system employing weakly coordinating anions.

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can destabilize the formation of this complex, thereby preventing the reaction from occurring. Most critically, sterically bulky alkenes bind less well to Cu(I) and thus are poor substrates for this strategy. ¹³ Consequently, many of the most interesting complex cyclobutane natural products cannot be efficiently synthesized using the Salomon–Kochi protocol or indeed by any known photocycloaddition methodology (Figure 1C). This represents a significant gap in chemists' ability to synthesize the diverse family of cyclobutane-containing natural products.

One notable consequence of the relative instability of the cationic copper bis(alkene) intermediate is a strong dependence on the coordinating ability of the counteranion. Salomon reported that photocycloadditions catalyzed by CuOTf occur at least an order of magnitude faster than those conducted using CuCl.⁹ This observation was attributed to the ability of more nucleophilic counteranions to displace the labile olefin ligands. We hypothesized that complexes bearing even more weakly coordinating counteranions (WCAs) than triflate would result in a more electrophilic Cu(I) metal center that could productively engage bulky alkenes in this reaction.

As a platform to test these ideas, we first examined the photocycloaddition of diene 1, which Salomon had reported was a poor substrate.13a Consistent with precedent, conditions that have most commonly been utilized for the Salomon-Kochi cycloaddition (1 mol% [Cu(OTf)]2•benzene) afforded only 28% of cyclobutane product (Table 1, entry 1). The reaction does not proceed to completion upon extended irradiation times, and the observation of Cu⁰ depositing in the reaction vessel indicated significant catalyst decomposition (entry 2). We imagined that Cu(I) complexes bearing even more weakly coordinating anions might increase the reaction rate. However, attempts to synthesize Cu(I) benzene complexes featuring a range of WCAs, either alone or in situ, were not successful due to the propensity of these unstabilized Cu(I) salts to undergo rapid decomposition. We wondered if alternate ancillary ligands might better stabilize the cationic Cu(I) center. Nitrogen and phosphine donor ligands commonly utilized in copper catalysis, however, have been shown to inhibit photocycloaddition, either by disfavoring formation of the bis(alkene) complex or by producing other low-energy chargetransfer excited states that outcompete formation of the requisite alkene MLCT state.12a,14

We hypothesized instead that a diene ligand such as cyclooctadiene (COD) might stabilize the highly electron-deficient Cu(I) center without engendering competitive low-energy charge-transfer states. Because displacement of a COD ligand by a less conformationally rigid bis(alkene) substrate would likely be thermodynamically unfavorable, known (COD)₂Cu(I) complexes¹⁵ seemed unlikely to be suitable precatalysts. We wondered instead if coordinatively unsaturated Cu(I) complexes could be generated *in situ* by anion metathesis of dimeric [Cu(COD)CI]₂ with Ag(I) salts of WCAs (Figure 1D). This strategy would enable use of bench-stable catalyst precursors in this reaction instead of the air- and moisture-sensitive [Cu(OTf)]₂•benzene complex that has been the catalyst of choice for this reaction for decades.

As a control, we first treated [Cu(COD)Cl]² with AgOTf *in situ*, and the resulting complex performed similarly to the standard [Cu(OTf)]²•benzene catalyst (entry 3). However, extended irradiation results in complete conversion, demonstrating that diene ligands are indeed able to stabilize the highly electrondeficient cationic Cu(I) center without attenuating its photoactivity (entry 4). We next examined the use of a series of WCAs in this reaction and were delighted to observe increased reactivity, with a correlation between the calculated gas-phase acidities¹⁶ of the WCA conjugate acids and the yield of the cycloaddition (entries 5–7). The optimal SbF₆⁻ complex afforded 94% yield of the [2+2] cycloadduct in just 1 h. Indeed, the reaction proceeds essentially to completion in only 30 min (entry 8), highlighting the substantial rate improvement using this optimal catalyst over the canonical triflate salt.

To test the importance of the Cu(I):COD stoichiometry, we next independently prepared $[Cu(COD)_2]SbF_6$ and found it to be a less effective catalyst (entry 9), consistent with the expected slow rate of exchange of the second COD ligand with substrate. Excess COD ligand also has a strong inhibitory effect on the cycloaddition (entry 10). Similarly, the use of CuCl as a precatalyst in the absence of COD ligand proved ineffective (entry 11).¹⁷ Finally, control experiments excluding the Cu catalyst, silver salt, or light source resulted in no observable consumption of the substrate (entries 12–14), demonstrating the necessity of each of these reaction components.

Table 1: Optimization of in situ catalyst generation with silver salts of WCAs

	0TBS [0 Me Me 0.025 M	Cu(I) cat. or Cu(COD)CI] ₂ /AgX Et ₂ O, 254 nm, 0.5-1 h		e OTBS
Entry	[Cu]	[Ag]	Time	Yield ^{a,b}
1	1 mol% [CuOTf] ₂ •C ₆ H ₆	-	1 h	28% 4:1 d.r.
2	1 mol% [CuOTf] ₂ •C ₆ H ₆	-	18 h	42% 4:1 d.r.
3	1 mol% [Cu(COD)Cl]2	AgOTf (299.5) ^c	1 h	33% 4:1 d.r.
4	1 mol% [Cu(COD)Cl]2	AgOTf (299.5) ^c	18 h	91% 4:1 d.r.
5	1 mol% [Cu(COD)Cl]2	AgBF ₄ (288.0) ^c	1 h	52% 4:1 d.r.
6	1 mol% [Cu(COD)Cl]2	AgNTf ₂ (286.5) ^c	1 h	57% 8:1 d.r.
7	1 mol% [Cu(COD)Cl] ₂	AgSbF ₆ (255.5) ^c	1 h	94% 4:1 d.r.
8	1 mol% [Cu(COD)Cl]2	AgSbF ₆	0.5 h	81% 4:1 d.r.
9	2 mol% Cu(COD) ₂ SbF ₆	-	0.5 h	18% 4:1 d.r.
10 ^d	1 mol% [Cu(COD)Cl] ₂ ,	AgSbF ₆	0.5 h	0%
11	2 mol% CuCl	AgSbF ₆	0.5 h	9%
12	1 mol% [Cu(COD)Cl]2	-	0.5 h	0%
13	-	AgSbF ₆	0.5 h	0%
14 ^e	1 mol% [Cu(COD)Cl]2	AgSbF ₆	0.5 h	0%

[a] Reactions conducted in quartz tubes equipped with a cold finger. Irradiation took place in a Rayonet RP-100 photoreactor with 254 nm bulbs. [b] NMR yields taken with TMS-Ph as internal standard. [c] Gas phase acidity constants of corresponding acid. [d] Reaction conducted in the presence of 50 mol% additional COD ligand. [e] No UV irradiation.

Studies examining the scope of the photocycloaddition using this new catalyst system are summarized in Table 2. We first examined the reactivity of variously substituted 1,6-heptadienes (2–8). As expected, the optimized [Cu(COD)Cl]₂/AgSbF₆ catalyst system outperforms the standard [Cu(OTf)]₂•benzene catalyst in all cases examined. This advantage became more evident with greater steric bulk on the alkene, consistent with our catalyst design strategy. Cyclization of naturally occurring terpenes linalool and nerolidol demonstrate

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Table 2: Scope and Comparison Studies for the Cu(I)-Catalyzed Photocycloaddition



[a] NMR Yields based on TMS-Ph internal standard; [Cu(OTf)]₂-benzene yields at same catalyst loading, concentration and timepoint; [b] Isolated yields; [c] gram-scale reaction;. [d] 2.5 mol% AgSbF_δ, 0.0125 M in Et₂O.

tolerance both for a free hydroxyl group and pendant substituted olefins (9-10). Interestingly, nerolidol cycloadduct 10 was isolated as a 1:1 mixture of diastereomers, despite the well-defined geometry of the starting alkene. Even with the increased Lewis acidity of the reactive Cu(I) center, a range of Lewis basic functional groups including amides, ethers, and alcohols are readily tolerated (11-15). The rate of reaction slowed using a chelating 1,3-diol-containing substrate (16), which required longer reaction time and higher catalyst loading. Protection of the diol, however, fully restores reactivity (17). Vinyl boronate esters also cyclize in good yield (18) without any observed unproductive deborylation, providing a synthetic handle for further derivatization. A range of common alcohol protecting groups were also investigated (19-23). A base-sensitive pivalate protecting group (19) is well tolerated. An acid-sensitive TES group can be utilized in place of TBS (20), albeit with somewhat diminished endo diastereoselectivity. Highly chelating MOM protecting groups are well tolerated (21). Furthermore, allyl carbonate with a third alkene binding site gives good yields without decomposition

of the protecting group (22). Interestingly, benzyl protecting groups are uniquely tolerated by the new catalyst system; we observed complete decomposition of this substrate when the reaction was conducted using CuOTf (23). For ease of synthesis, many of the substrates examined bear oxygen substituents in the allylic position. Regardless of the alkene substitution or the identity of the allylic coordinating functional group, the cycloaddition preferentially results in the formation of the thermodynamically less favourable anti-cycloadduct. This result is consistent with Salomon's observations using allylic alcohol substrates, suggesting a chelating interaction with the Cu(I) center in the reactive complex.13b Finally, these reaction conditions were found to be readily scalable: a batch reaction conducted on gram-scale afforded 3 in 89% yield after 5 h of irradiation.

Given the observation that geometrically well-defined alkene substrates result in the formation of diastereomeric products, we became interested in the origin of the loss of stereochemical integrity. First, we prepared the *trans* and *cis*

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isomers of O-allyl but-2-ene-1,4-diol and irradiated them under the optimized reaction conditions. Both afford a mixture of diastereomers in good yields, but importantly, the identity of the major diastereomer differs (Scheme 3). For a more detailed insight, we conducted a time-course experiment using *cis* isomer **28**. We observed the formation of *trans* alkene **26** over the course of this experiment, and the rate of its formation is competitive with the production of the cycloadducts.¹⁸ Furthermore, the alkene isomerization occurs only upon irradiation. We conclude, therefore, that the cycloaddition itself is stereospecific, and that the loss of stereochemical fidelity is due to an alternate Cucatalyzed photoreaction that scrambles the geometry of the starting alkene.



Scheme 3. Origins of observed diastereoselectivity.

The enhanced reactivity of this new catalyst system, particularly towards substituted alkene substrates, significantly expands the applicability of photocycloaddition methodology to the synthesis of a broader class of complex cyclobutane natural products. To highlight this potential, we used this new method to prepare the core of the natural product sulcatine G¹⁹ in 98% yield. As expected, the improved method provides significantly superior results compared to [Cu(OTf)]•benzene (Scheme 4a). Importantly, this reaction favors formation of the highly sterically disfavored *anti* configuration of the bridgehead substituents (**30**) due to allylic hydroxyl coordination, a key structural feature of this molecule. We also prepared the core of perforatol²⁰ in high yield and as a single diastereomer (**32**), the new catalyst again showing faster rates of cycloaddition (Scheme 4b).

¹ From a search of the *Reaxys* database (Sep 26 2020)



Scheme 4. Cyclization of Sterically Hindered Natural Product Cores 3.

In summary, we have developed a new catalyst system that extends the useful scope of the Cu-catalyzed Salomon-Kochi photocycloaddition reaction, enabling the cycloaddition of sterically encumbered substituted alkenes. Two features are critical to the success of this strategy. First, the use of a weakly coordinating SbF6⁻ counteranion increases the reactivity of the catalyst by favoring the formation of the requisite copper:bis(alkene) complex. Second, while weakly coordinated cationic Cu(I) salts are prone to decomposition under the reaction conditions, a COD ligand can stabilize the Cu(I) center without engendering the unproductive competitive low-energy LMCT transitions that would be introduced using more traditional nitrogen or phosphorous ligands. The optimal catalytic complex is capable of engaging hindered polysubstituted alkene substrates, can be generated from bench-stable precursors, and enjoys greater stability compared to the standard [Cu(OTf)]2•benzene precatalyst. The preparation of the cores of the natural products sulcatine G and perforatol demonstrate the utility of this reaction in accessing structurally complex cyclobutane natural products.

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Keywords: alkene ligands • copper • cycloaddition • cyclobutanes • photocatalysis

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We describe herein a new catalytic method for the [2+2] photocycloaddition of simple aliphatic alkenes. The Cu(I) catalyst features a weakly-coordinating anion that enable the formation of a long-lived Cu-bis(alkene) complex and supporting olefin ligands that stabilize the cationic Cu(I) center without disrupting its photochemistry. This catalyst enjoys increased reaction rates and substrate scope compared to previous Cu-templated photocycloaddition methods.

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