Intermolecular 2+2 Imine-Olefin Photocycloadditions Enabled by Cu(I)-Alkene MLCT

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Abstract: 2+2 Photocycloadditions are idealized, convergent approaches to the construction of 4-membered heterocyclic rings, including azetidines. However, methods of direct excitation are limited by the unfavorable photophysical properties of imines and electronically unbiased alkenes. Here, we report copper-catalyzed photocycloadditions of non-conjugated imines and alkenes to produce a variety of substituted azetidines. Ligand design allows this base metal-catalyzed method to achieve 2+2 imine-olefin photocycloaddition via selective alkene activation through a coordination-MLCT pathway.

Nitrogen heterocycles are prevalent motifs in small molecule pharmaceuticals and their rapid construction continues to drive new reaction development.¹ While 3-, 5- and 6-membered *N*-heterocycles are exceptionally common, made possible by a variety of synthetically accessible routes for their construction, 4-membered heterocycles are scarce by comparison despite the promising biological activity displayed by many azetidine-containing compounds.^{2,3,4,5,6,7} The 2+2 photocycloaddition of two π -components is a prototypical approach to 4-membered ring construction. While limited in generality, the Paternò-Büchi reaction forms oxetanes through direct irradiation of a carbonyl C=O double bond followed by C=C double bond capture.^{8,9,10} Aza-Paternò-Büchi analogs using imines in place of aldehydes or ketones do not generally result in the formation of azetidines due to the low barrier *E/Z* isomerization available upon excitation of the imine C=N double bond.¹¹ Maruoka reported a rare intermolecular azetidine-forming 2+2 photocycloaddition example using naphthyl derived *N*-sulfonyl aldimines and styrene or benzofuran (Figure 1A).¹² However, this reactivity was exclusive to these substrate pairs and was enabled by a pi-stacking association of the substrates prior to excitation. Alternative strategies that overcome the challenge of imine isomerization have used cyclic imines which cannot undergo *E/Z* isomerization,^{13,14,15} via preferential excitation of a conjugated C=C double bond tethered to an imine,^{16,17} or both (Figure 1B). Despite these advances, catalyst-controlled approaches to 2+2 imine-olefin photocycloaddition (IOPC) remain limited as general strategies for azetidine construction.

Fig. 1. C=N Bond 2+2 photocycloadditions.

^aSee ref. 12. ^bSee refs. 13-14,16-17. ^cSee ref. 15.

Transition metal compounds capable of photoexcitation via metal to ligand charge transfer (MLCT) to achieve intermolecular electron or energy transfer have recently gained significant recognition for their use in chemical synthesis.^{18,19,20,21} Meggers reported photochemical cyclobutane synthesis by in situ formation of the active chromophore as a chiral at metal, O-bound Rh-enone compound.²² Yoon achieved enantioselective 2+2 photocycloaddition of conjugated alkenes to form cyclobutanes via Dexter energy transfer through H-bonding and π - π interactions of substrate 3-alkoxyquinolones and Ir-based photocatalysts.²³ We recently reported a Cu-catalyzed 2+2 carbonyl-olefin photocycloaddition approach for oxetane formation by inverting conventional Paternò-Büchi reactivity and achieved alkene activation via coordination followed by MLCT.²⁴ We hypothesized that 2+2 imine-olefin photocycloadditions (IOPC) may be achieved to access azetidines by coordination and MLCT with either the alkene or imine π -component (Figure 1C).

To assess this hypothesis, we irradiated a 1:3 mixture of *N*-butyl-2-methylpropan-1-imine (**1**) and norbornene with catalytic hydrotris(pyrazolyl)borate copper(I) (**TpCu**) in diethyl ether using a 100 W Hg lamp for 8 h which resulted in formation of the corresponding azetidine **1A** in 31% yield with exclusive *exo* selectivity (Table 1, entry 1). Removing either **TpCu** or any light source both resulted in no appreciable formation of **1A** (entries 2 and 3). Using a small excess of imine relative to norbornene (1.1:1) improved reaction efficiency (entry 4), while using a 3-fold excess of **1**, produced **1A** in 79% yield (entry 5). Application of a 300 nm cut-on filter resulted in a significant decrease in the yield of **1A** to 39% even after a prolonged 36 h reaction time suggesting that product forming irradiation occurred at wavelengths shorter than 300 nm (entry 6). Using CuCl or CuOTf in place of **TpCu** did not result in any detectable quantities of **1A** (entries 7 and 8), underscoring the importance of the coordination environment of the Cu(I) source used.

Reaction optimization:

Entry	deviation from standard conditions	Yield of 1A ^a
1	none	31% ^b
2	no TpCu	<5%
3	no light	<i>n.d.</i>
4	1.1 equiv 1 , 1 equiv norbornene	55%
5	3 equiv 1 , 1 equiv norbornene	79%
6	entry 5 with 300 nm cut-on filter	39% ^c
7	CuCl (20 mol %) in place of TpCu	<i>n.d.</i>
8	CuOTf (20 mol %) in place of TpCu	<i>n.d.</i>

Table 1. Summary of reaction optimization studies.

^a**1A** was detected as a >95:5 *exo:endo* mixture and 62:48 diastereomer mixture at C2 in all experiments; yields determined by ¹H NMR analysis of crude reactions using durene as an internal standard. ^bReaction time 8 h due to consumption of **1**. ^cReaction time 36 h.

In exploration of imines that similarly undergo Cu-catalyzed 2+2 IOPC with norbornene, we found that aldimines from *N*-allyl amine and isobutyraldehyde, 3-(methylthio)propanal, and melonal all successfully were converted to their corresponding azetidines, **2**, **3**, and **4**, respectively, in good to excellent yields (Figure 2). Imines bearing cyclopropyl groups participated in this 2+2 IOPC to produce azetidines exclusively without the detection of cyclopropyl ring-opened products (**5** and **6**).^{25,26} While imines derived from acetophenone, benzaldehyde, or aniline did not participate in this 2+2 IOPC, a phenethylamine derived

isobutyraldimine, produced azetidine **7**, suggesting that arene groups are tolerated when not conjugated to the imine. Heterocycles including tetrahydrofuran (**8**), thiophene (**9**), and morpholine (**10**) as well as an acyclic 3° amine (**12**) were all well tolerated in this process. Productive 2+2 IOPC was particularly notable in the presence of a γ -lactam (**11**), showcasing the chemoselectivity of olefin activation even in the presence of other π -components capable of absorbing UV light. Imines derived from ketones also reacted efficiently to produce the corresponding azetidines even when the imine also contained Lewis-basic 3° amine (**13**), acetal (**14**), or ether (**15**) functionalities.

Fig. 2. 2+2 Imine-Olefin photocycloaddition reaction scope.

All reactions carried out with 1 equiv norbornene, 1.1 equiv imine, 20 mol % **TpCu**, in diethyl ether (0.15 M) and irradiated with a 100 W Hg lamp; all yields are of isolated material following purification via

basic alumina chromatography and diastereomeric ratios were determined via gas chromatography of crude reaction mixtures; all products detected as >95:5 *exo:endo* diastereomers. ^a3 equiv of imine used.

^bYield in parentheses obtained without **TpCu**.

Biologically active azetidines such as penaresidin A, nicotianamine, medicanine, and mugineic acid feature *N*-alkyl groups or are unsubstituted at nitrogen, but access to these 2° azetidines can be challenging using existing cyclization methods that require *N*-substituents that are stubborn or not amenable to cleavage. This Cu-catalyzed 2+2 IOPC is uniquely capable of engaging *N*-alkyl imines directly as well as *N*-substituents that are easily removed. *N*-Allyl azetidine **13** underwent deallylation to reveal the corresponding 2° azetidine in 82% yield using 2 mol % Pd(PPh₃)₄ and 2-mercaptobenzoic acid. Alternatively, cyclohexanone *O*-methyl oxime also performed well as an imine component in this 2+2 IOPC, delivering the corresponding *N*-methoxy azetidine **19** from which facile reductive N-O bond cleavage using activated Zn dust in aqueous acetic acid to provide the corresponding unsubstituted azetidine in 93% yield.

Diversification of the olefin component allowed norbornene derivatives containing acetyl, vinyl, cyano, and *tert*-butyltrimethyl silyl ether groups to be successfully coupled with *N*-allyl cyclopentanimine (**20-24**). The identity of azetidine **23** was unambiguously confirmed through determination of the solid-state structure of its hydroiodic salt using X-ray diffraction (Figure 2, **23-HI**).

While maleic anhydride is known to undergo selective cyclobutane forming 2+2 photocycloaddition with ethylene using acetophenone as a photosensitizer,²⁷ direct excitation of maleic anhydride with *N*-allyl cyclopentanimine resulted in the formation of azetidine **25** in 51% yield along with a complex mixture of unidentified byproducts. Subjecting the same reactant pair to irradiation in the presence of 20 mol % **TpCu** resulted in the exclusive formation of **25** in 98% yield. Similarly, other imines were converted to the corresponding maleic anhydride azetidines (**26** and **27**) but the use of **TpCu** uniformly increased both reaction efficiency and selectivity. *N*-Methyl maleimide was also successfully converted to the corresponding azetidine **29** with *N*-allyl cyclopentanimine in 49% yield.

We initially hypothesized that 2+2 IOPC could occur through activation of either the imine or alkene π -bond; through a combination of ¹H NMR and electronic absorption spectroscopies observed the same requirement of alkene coordination to **TpCu** for azetidine formation was observed analogously to our Cu-mediated 2+2 carbonyl-olefin photocycloaddition studies.²⁴ **TpCu-NB** was isolated as a white crystalline solid in 87% yield upon mixing equimolar amounts of **TpCu** and norbornene in THF and the solid-state structure determined by single crystal X-ray diffraction (Figure 3A and B). The coordination geometry of the complex is best described as pseudo-tetrahedral about the Cu-ion. The carbon-carbon bond distance of the coordinated olefin (1.387 Å) is similar to that found in other Cu(I)-norbornene compounds (1.36-1.39 Å) indicative of a predominating σ -bonding, rather than π -back-bonding, metal-olefin coordination

interaction.^{28,29,30,31} Examination of the Cu-N(pyrazolyl) bond distances reveal that while two were nearly equivalent (Cu-N(2) = 1.999(2), Cu-N(4) = 2.010(2)), the third was significantly longer (Cu-N(6) = 2.274(2)), breaking the C₃ symmetry axis of the hydrotris(pyrazolyl)borate chelate.

Fig. 3. Spectroscopic investigations of 2+2 IOPC reaction intermediates.

A. Synthesis of hydrotris(pyrazolyl)borate copper olefin compounds. **B.** X-ray structures of the norbornene and maleic anhydride complexes **TpCu-NB** and **TpCu-MA**. **C.** Electronic absorption spectra of reaction components and transmission spectrum of reaction vessels used.

The maleic anhydride adduct, **TpCu-MA**, was similarly prepared and crystallographically characterized. The coordination geometry of the complex is analogous to that of **TpCu-NB** and while the carbon-carbon bond length of the coordinated maleic anhydride (1.390 Å) is elongated compared to the free olefin (1.3032 Å),³² it is short compared to the only other structurally characterized Cu(I)-maleic anhydride compound which is supported by an iminophosphanamide chelate (1.49 Å),³³ suggesting that the bonding in **TpCu-MA** is analogous to that observed in **TpCu-NB**. While ligand exchange was observed by ¹H NMR spectroscopy from **TpCu-NB** in the presence of the imines used in our study, isolation of a **TpCu-imine** coordination compound was unsuccessful likely due to the observed rapid ligand exchange. However, coordinated maleic anhydride was not analogously displaced by imines of this study, facilitating further mechanistic investigations with this system.

The electronic absorption spectra of ethereal solutions of individual 2+2 IOPC reaction components showed no distinct absorption features 250-400 nm and the transmission spectrum of the borosilicate glass reaction vessels used in this study indicated that light below 280 nm is largely filtered from reaching the reaction mixture (Figure 3C). Combined with the 300 nm cut-on filter results (Table 1, entry 6), this supports that azetidine formation predominately occurs via excitation between 280-300 nm. Conversely, a stoichiometric solution mixture of **TpCu** and maleic anhydride resulted in an electronic absorption spectrum with a broad feature with a maximum at 263 nm, which is very similar to the spectrum observed of **TpCu-NB** and is nearly identical to the spectrum of a stoichiometric mixture of **TpCu**, maleic anhydride and imine **1**. While neither **1** nor norbornene showed significant absorptions above 250 nm, maleic anhydride did, rationalizing the small amount of non-catalyzed background photocycloaddition observed with this alkene.

Fig. 4. 2+2 IOPC mechanistic proposal

A calculated electronic absorption spectrum of **TpCu-NB** best approximated the experimentally observed spectrum using time-dependent density functional theory (DFT) calculations of at the M06 level of theory with the Tamm-Dancoff approximation. This enabled the construction of qualitative molecular orbital diagrams for **TpCu-NB** at the observed absorption feature 250-300 nm linked to azetidine formation (see the Supporting Information for additional details). The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of **TpCu-NB** are primarily **TpCu**-based and olefin(π^*)-based, respectively (Figure 4). This is supported by prior DFT calculations that concluded that MLCT of idealized cationic Cu(I)-ethylene compounds was responsible for cyclobutane forming 2+2 photocycloadditions.³⁴ This excited state selectively then captures the imine C=N group affording the azetidine product. Chemoselectivity of azetidine formation over alkene dimerization pathways is attributed to the known rapid rates of C-centered radical addition to C=N double bonds³⁵ and preference over alkene addition.²⁵

In conclusion, we report herein an intermolecular 2+2 photocycloaddition of aliphatic imines and alkenes to form azetidines. The use of hydrotris(pyrazolyl)borate copper(I) as a pre-catalyst allows for coordination of the olefin component and selective absorption of light 280-300 nm. A combination of solution ¹H NMR

and electronic absorption spectroscopies along with DFT calculations from solid-state structural information supports that Cu(*d*) to olefin(π^*) MLCT leads to azetidine formation. This work highlights a catalyst controlled 2+2 imine-olefin photocycloaddition strategy that selectively activates π -components at red-shifted wavelengths compared to uncoordinated substrates.

Acknowledgments

We thank Christine Lee and Jacob Hawver-Patcher for preliminary assistance in imine synthesis, the Tor group at UCSD for usage of their UV-vis spectrometer, and Glen Junor for assistance with DFT calculations.

Funding

This work was supported by start-up funds provided by the University of California San Diego, National Science Foundation CAREER Award No. 1945463, and the American Chemical Society Petroleum Research Fund grant 60135-DN11.

Author contributions

D.M.F. carried out the synthetic work, analytical characterization, spectroscopic and computational studies. M.L.N. carried out the crystallographic studies. V.A.S. assisted with data analysis and directed the research. V.A.S. wrote and edited the manuscript, with input from all authors.

Competing interests

Authors declare no competing interests.

Data and materials availability

X-ray data are available free of charge from the Cambridge Crystallographic Data Centre under references CCDC-1986944 (**23-HI**), CCDC-1986945 (**TpCu-NB**), CCDC-1986946 (**TpCu-MA**). Additional synthetic, spectroscopic, crystallographic, and computational data are included in the supplementary materials.

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