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Radical-Polar Crossover Annulation: A Platform for Accessing Polycyclic Cyclopropanes

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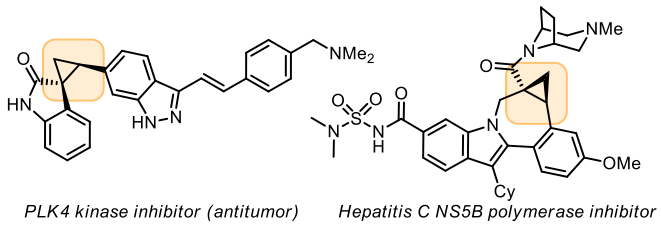
Abstract. Photoredox-mediated radical/polar crossover (RPC) processes provide unique solutions to challenging annulations. Herein, we describe an approach to the cyclopropanation of olefins that are embedded within bicyclic scaffolds. Whereas these systems are notoriously recalcitrant toward classical cyclopropanation approaches, RPC cyclopropanation can be executed with ease, leading to polycarbocyclic and polyheterocyclic cyclopropanes. The cyclopropanation proceeds through a photoredox-enabled Giese-type radical addition followed by an intramolecular anionic substitution reaction on a neopentyl leaving group.

Keywords: Cyclopropanes; Photoredox Catalysis; Cyclization; Radical/Polar Crossover; Radicals

Introduction

The cyclopropane scaffold is of longstanding interest because of its unique structural attributes and frequent occurrence in bioactive molecules. Consequently, substantial efforts have been made in developing cyclopropanation strategies.[1] Inclusion of the cyclopropyl motif in polycyclic, bioactive molecules has been demonstrated to increase their rigidity, potency, and metabolic stability



PLK4 kinase inhibitor (antitumor) *Hepatitis C NS5B polymerase inhibitor*

Figure 1. Examples of polycyclic α-aryl cyclopropanes with bioactive properties.

because of the stronger, shorter cyclopropyl C-H bonds.[2] Cyclopropanes adjacent to aromatic rings can serve as isosteres of styrenes with improved metabolic stability. Several polycyclic cyclopropanes with this substructure have been reported by pharmaceutical companies and academic groups for antiviral (hepatitis C),[3] antitumor,[4] and anti-neurodegenerative[5] indications.

The polycyclic cyclopropane scaffolds reported in these and other studies are commonly accessed through the cyclopropanation of styrene precursors, typically with carbene or sulfur ylide chemistry (Figure 2).[6] Aside from the need to have a predetermined cyclopropane structure (i.e., the cyclopropane substituents must be pre-installed as a polysubstituted alkene), these traditional methods possess inherent limitations. The classical Simmons-Smith cyclopropanation, although robust and well-proven, is sluggish with polysubstituted styrenes[5] and generally intolerant of Lewis basic functional groups (such as pyridines), although these limitations can be overcome in certain cases.[1],[6] The Corey-Chaykovsky method has been used for the synthesis of α-aryl cyclopropanes such as those shown in

Figure 1, but these reactions require an activated alkene acceptor and strong bases that can limit functional group tolerance. Inter-[5],[7] or intramolecular[8] cyclopropanation with diazo species has also been used to access polycyclic cyclopropane scaffolds; however, these reactions sometimes pose operational and selectivity challenges. Several intermolecular cyclopropanation methods have recently been developed that provide facile alternatives to these methods.[9]

In the course of our studies on the development of bench-stable radical precursors for application in photoredox catalysis,[10] we have identified an alternative cyclopropanation approach we refer to as radical/polar crossover (RPC) annulation. The initial work in this area made use of an iodomethylsilicate reagent that served as a formal carbene equivalent for the cyclopropanation of α-CF_3-substituted alkenes, acrylates, and styrenes.[11] More recent studies revealed that homoallylic tosylates can undergo cyclopropanation when irradiated with visible light in the presence of a radical precursor reagent.[12] Both reaction classes are proposed to proceed through radical addition to an alkene, single electron reduction of the radical adduct to an anion, and anionic 3-*exo*-*tet* ring closure. Though the mechanisms of these two reaction classes are convergent, the latter benefits from a modular character (i.e., different subunits of the 1,1-disubstituted cyclopropane can be introduced from the two respective partners).

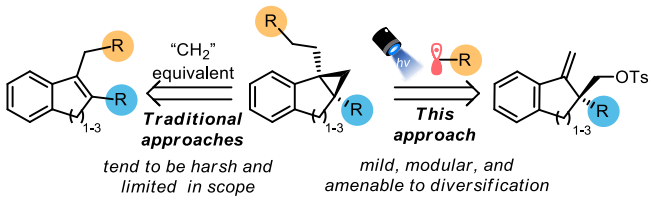
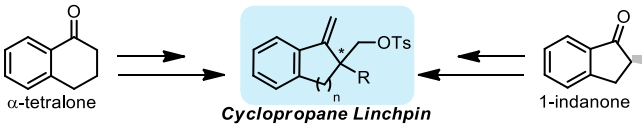


Figure 2. Comparison and context of current work.

Motivated by the success of these mild, operationally simple radical/polar crossover reactions, we sought to address the synthesis of highly substituted cyclopropanes that are challenging to access. The success of such a proposition would largely be dependent on the success of anionic cyclization on a neopentyl center. To test the feasibility of this approach, we designed a series of olefins that could serve as linchpins to construct an array of polycyclic cyclopropanes. Treatment of these substrates with photocatalytically-generated radicals would provide access to tetra-substituted, polycyclic cyclopropanes (Figure 2) that would be challenging to access by state-of-the-art approaches. Further, the process should accommodate multiple radical sources, thus allowing easy access to bicyclic cyclopropanes with diverse functional groups. The reaction effectively highlights the utility of single-electron pathways in accomplishing otherwise challenging or harsh transformations.[13]

Results and Discussion

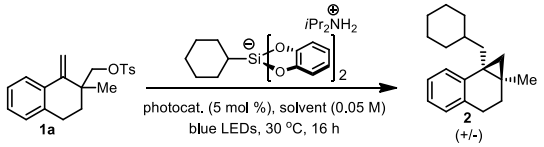
The requisite cyclopropanation substrates were prepared through a straightforward sequence starting from commodity ketones such as α-tetralone or 1-indanone (Scheme 1). The known β-ketoesters derived from these ketones were alkylated with electrophiles such as iodomethane or benzylic



Scheme 1. Commodity ketones to cyclopropane linchpins.

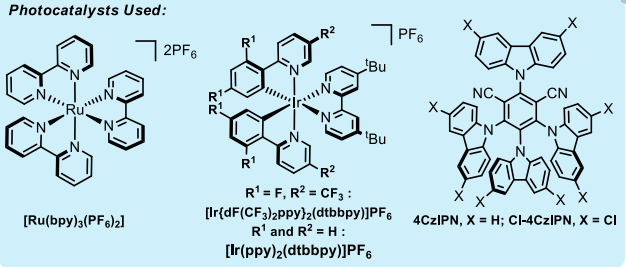
bromides. Enantioselective alkylation of these ketoesters has been demonstrated using enantioselective phase transfer catalysis,[14] and this strategy could be employed to set the absolute stereochemistry of the

Table 1. Optimization of the radical/polar crossover cyclopropanation process.[a]



entry	Solvent	Photocatalyst	1a/IS	2/IS
1	MeCN	**Cl-4CzIPN**[b]	1.21	0
2	MeCN	**4CzIPN**[c]	0.93	0
3	MeCN	**$[Ru(bpy)_3](PF_6)_2$**	0.64	0
4	MeCN	**$[Ir\{dF(CF_3)_2ppy\}_2(dtbbpy)]PF_6$**	1.01	0
5	MeCN	**$[Ir(ppy)_2(dtbbpy)]PF_6$**	1.02	0.074
6	DMSO	**Cl-4CzIPN**	0.77	1.40
7	DMSO	**4CzIPN**	0.27	1.31
8	DMSO	**$[Ru(bpy)_3](PF_6)_2$**	1.11	1.63
9	DMSO	**$[Ir\{dF(CF_3)_2ppy\}_2(dtbbpy)]PF_6$**	1.14	1.52
10	DMSO	**$[Ir(ppy)_2(dtbbpy)]PF_6$**	0.45	0.94
11	acetone	**Cl-4CzIPN**	0.89	0
12	acetone	**4CzIPN**	0.95	0
13	acetone	**$[Ru(bpy)_3](PF_6)_2$**	0.82	0.07
14	acetone	**$[Ir\{dF(CF_3)_2ppy\}_2(dtbbpy)]PF_6$**	0.96	0
15	acetone	**$[Ir(ppy)_2(dtbbpy)]PF_6$**	0.76	0.10
16[d]	DMSO	**4CzIPN**	1.12	0
17	DMSO	**None**	1.22	0

Photocatalysts Used:



[a]Optimization reactions performed using 0.025 mmol of **1a** in the presence of 4,4′-di-*tert*-butylbiphenyl as internal standard (IS) (0.0125 mmol) for 16 h at 30 °C; Ratios of **1a**

and **2** to IS determined by HPLC analysis of the crude reaction mixture. [b]2,4,5,6-Tetrakis(3,6-dichloro-9H-carbazol-9-yl)isophthalonitrile. [c]2,4,5,6-Tetra(9H-carbazol-9-yl)isophthalonitrile. [d]Reaction conducted in the absence of light.

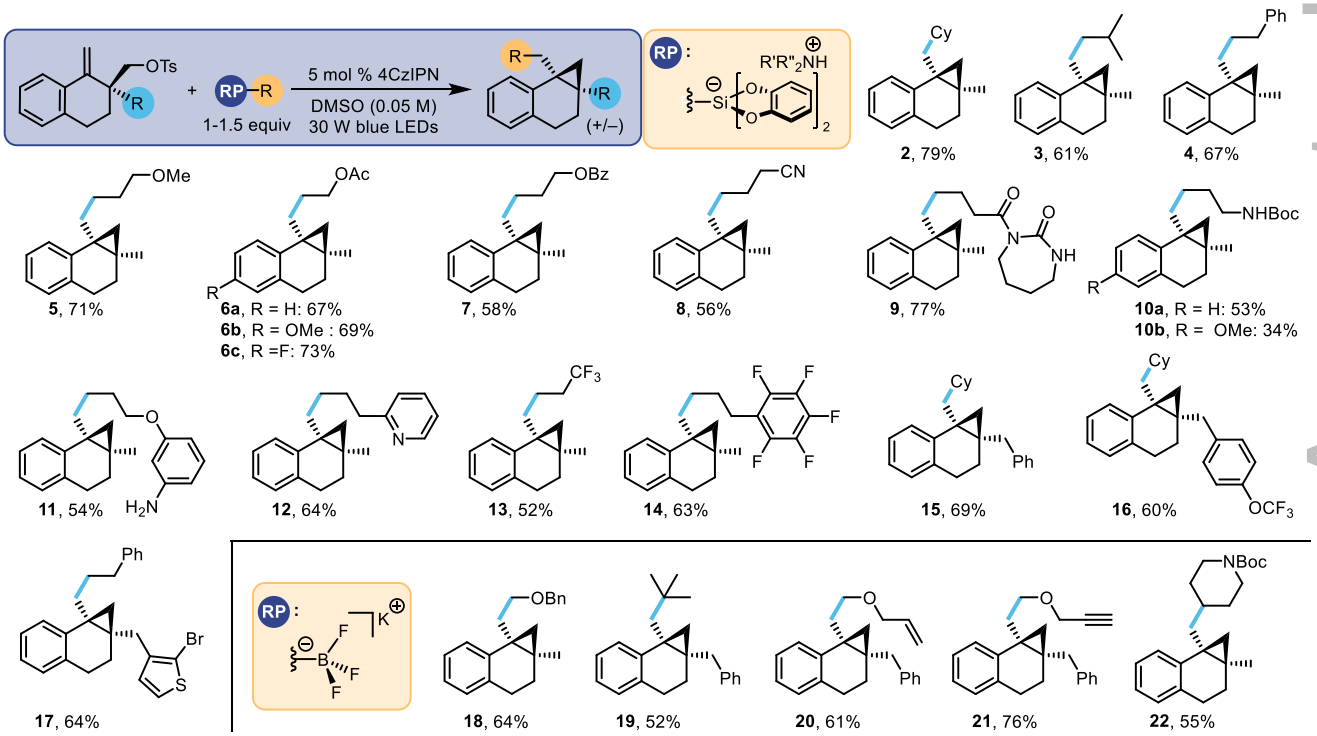
linchpin, and ultimately, the resulting tetra-substituted cyclopropane. A series of simple, high-yielding steps (Wittig olefination of the ketone, reduction of the ester, and tosylation of the resulting alcohol) provided the requisite cyclopropanation substrates.

An assessment of pertinent reaction parameters was conducted (Table 1). Suitable reaction conditions were identified through screening using **1a** as a model linchpin and bis(catecholato)cyclohexylsilicate as a model radical precursor (RP). An alkylsilicate was selected because such species are versatile radical forebears[15] that readily furnish both 1° and 2° alkyl radicals with an array of photocatalysts, and various parameters for their use are less restrictive than other RP classes. Moreover, they produce benign by-products that would not impede nor degrade cyclopropane **2**. Solvents that have proven adequate for radical generation using alkylsilicates were assessed, and ultimately, DMSO was found to be the most suitable solvent, likely because of the polar nature of the anionic transition state for cyclization. Ultimately, 4CzIPN[16] proved to be the ideal photocatalyst (especially considering the high conversion, low cost of the catalyst, and its metal-free nature), and no additives were required. Further, these conditions proved broadly applicable over a range of substrates and for larger scale reactions. Control reactions confirmed that this was indeed a photocatalyst-driven process, requiring both the photocatalyst and irradiation to effect cyclopropanation.

The developed conditions were applied to the cyclopropanation of tetralone-derived tosylates. Various sterically disparate alkyl fragments were appended to the olefin and used to facilitate the ring-closing cascade. Protic functional groups (**9-11**) and heterocycles (**12, 17**) posed no problem to the cyclopropanation reaction. The reaction also tolerated a polyfluorinated arene without evidence of products derived from radical/polar S_NAr-type processes.[17] Alteration of the tetralone structure was similarly well-tolerated and allowed various groups to be installed on the cyclopropane fragment (**16, 17**) as well as on the arene (**6b-c**, **10b**) emphasizing the modular nature of this approach. Electronic changes on the aryl ring appear to have little impact on cyclopropanation reactivity, as evidenced by the lack of variablity in yield between **6a-6c** and the results of a head-to-head competition study (See Supporting Information). Our previous studies on the photoredox cyclopropanation of acyclic systems showed that the electronics of the arene contribute substantially to reaction success, whereas for the rigid systems investigated here, the influence of electronics is minimal.[11],[12]

To augment the modularity of this approach, alternative RPs such as organotrifluoroborates could be used in place of alkylsilicates without any need for

Table 2. Cyclopropanation of the tetralone-derived core via RPC.[a]

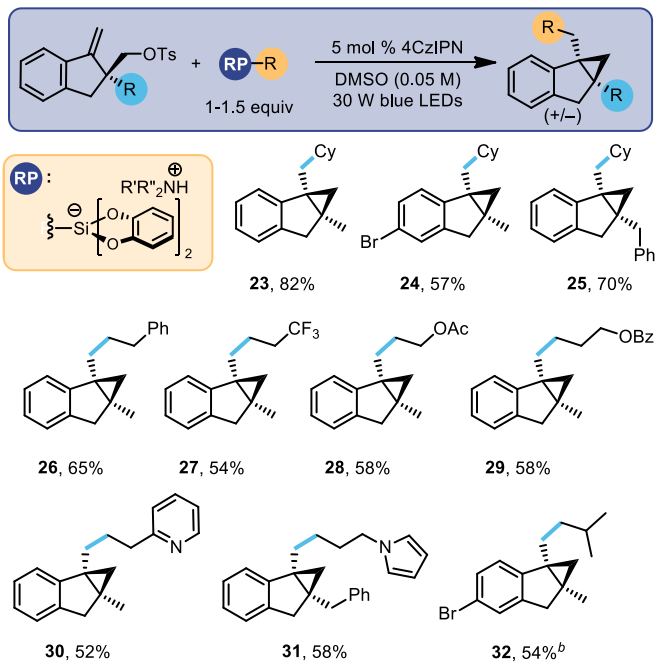


[a]Unless otherwise noted, the reactions were carried out on a 0.2-0.3 mmol scale of the corresponding tosylate at 30 °C for 2-16 h; RP = radical precursor; isolated yields after purification, see Supporting Information for details regarding purifications and alterations to radical precursor loading.

re-optimization. Using these alternate radical progenitors, an array of complex oxygen-containing fragments could be installed. Other 2° and 3° alkyl radicals generated from alkyltrifluoroborates were also used to install *tert*-butyl (**19**) and heterocyclic (**22**) motifs on the polycyclic core. In the case of the latter, both quaternary and tertiary centers were set in a singular operation. Given the inherent diastereospecific nature of this reaction, enantioselective alkylation of the requisite starting materials would thereby render this process an enantiospecific means to generate these cyclopropanes.

A series of indanone-derived tosylates were assembled in an analogous manner and subjected to the cyclopropanation process (**Table 3**). As with the tetralone-based system, radical addition followed by anionic ring closure occurred to provide an array of heretofore unknown polycyclic cyclopropanes. Fragments containing heterocycles, fluorinated motifs, and synthetically useful functional handles were all introduced with ease. Likewise, alteration of the structure of the cyclopropanation linchpin did not substantially impact the propensity for cyclopropanation. The use of a brominated indanone variant provided polycyclic cyclopropane **24** that could be diversified through traditional cross-coupling. Scale-up of this process posed no issue and gave a comparable yield to that of smaller scale cyclopropanations.

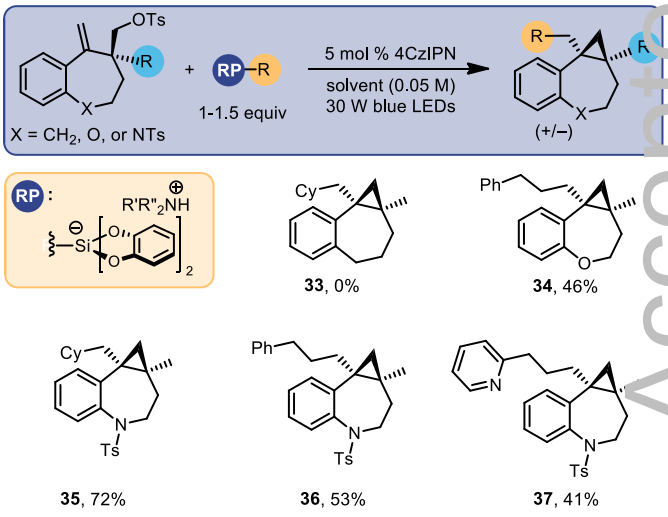
Table 3. Cyclopropanation of the indanone-derived core via RPC.[a]



[a]Unless otherwise noted, the reactions were carried out on a 0.2-0.3 mmol scale at 30 °C for 2-16 h; isolated yields after purification, see Supporting Information for details regarding purifications and alterations to radical precursor loading. [b]Reaction conducted on 1.2 mmol scale.

In an effort to elucidate the limitations of this approach toward polycyclic cyclopropanes, the preparation of larger bicyclic systems was attempted (**Table 4**). In initial efforts with a benzocycloheptanone-derived cyclopropanation linchpin, somewhat discouraging results were obtained. The cycloheptanone-based tosylate (and even its mesylate) mostly failed to react and produced very low amounts of the desired cyclopropane product and unknown alkene byproducts. No significant degradation occurred when the sample containing the tosylate was irradiated in the presence of 4CzIPN but in the absence of a radical precursor. It was noted that, unlike the tosylates of the indanone and tetralone systems, the cycloheptanone based system has unusual broadening of the ^{1}H NMR signals of this tosylate (and mesylate) and a distinctly different chemical shift for the alkenyl protons. This suggests that the radical addition or stability of the resulting benzylic radical may be impacted by conformational variation within this ring system, providing a possible explaination for the lack of reactivity.

Table 4. Cyclopropanation of larger ring sizes via RPC.[a]



[a]Unless otherwise noted, the reactions were carried out on a 0.2-0.3 mmol scale at 30 °C for 2-16 h; isolated yields after purification, see Supporting Information for details regarding purifications and alterations to radical precursor loading.

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At this juncture, we posited that the introduction of heteroatoms in the ring architecture would not only be feasible, but perhaps beneficial for restricting or changing the conformation of the ring. As such, benzoazepines and benzoxepines were examined. The requisite tosylates of these systems were readily prepared from commodity salicylate or anthranilic acid derivatives on multi-gram scale. Subjecting these tosylates to the established conditions for annulation led to facile cyclopropanation, albeit in somewhat lower yield than their smaller carbocyclic congeners.

Although a mild strategy for polycyclic cyclopropane construction, this approach is not without limitations. Clearly, conformation is critical for the success of cyclization. The conformationally rigid tetralone- and indanone-based systems underwent cyclopropanation with ease. Further, synthetic limitation can hamper this approach. For example, attempts to prepare the iodide, bromide, or chloride of the aforementioned cycloheptanone system were met with failure because of the steric constraints of displacement on a neopentyl leaving group. Likewise, because of the rather sterically congested nature of the transition state, attempts using 2° tosylates were met with failure. In addition, attempts to install other electrophilic fragments beyond methyl, benzyl and allyl were met with significant difficulty using the streamlined route devised from commodity precursors. However, when these systems were prepared (e.g. ethyl or homoallyl in place of methyl), successful cyclopropanation was observed.

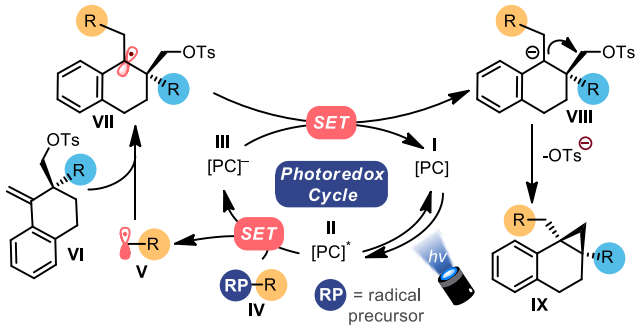

Figure 3. Proposed mechanism for cyclopropanation.

Regardless of the radical precursor or ring linchpin used, the mechanism of this process is presumed to proceed via the following series of events (Figure 3): 1) Photoexcitation of the photocatalyst **I** (in this case 4CzIPN) to its excited state **II**; 2) Reductive quenching of the excited photocatalyst by single electron transfer (SET) oxidation of the appropriate radical precursor **IV**; 3) Homolytic fragmentation of the radical precursor to generate an alkyl radical **V**; 4) Installation of the alkyl fragment via Giese-type addition of the generated radical to linchpin **VI**; 5) Reduction of the resulting α-aryl radical to generate the corresponding α-aryl anion **VIII**; 6) Anionic cyclization by displacement of the tosylate, resulting in C-C bond formation (and thus formation of a strained bicyclic system **IX**). It is likely that ring conformation can be determinant of reaction success, impacting both the radical addition and anionic cyclization.

Conclusion

The modular cyclopropanation strategy described here affords easy access to previously difficult to access and medicinally relevant polycyclic systems under mild conditions. Using commodity materials, an array of bench-stable linchpins can be assembled that are poised for cyclopropanation. The described radical/polar crossover approach thus enables these linchpins to be appended with an array of fragments while simultaneously triggering annulation. The radical source has a minimal effect on the success of cyclopropanation. This process ultimately provides a mild, metal-free strategy for assembling an array of diverse polycyclic stuctures containing the cyclopropyl motif.

Experimental Section

To an 8 mL reaction vial equipped with a stir bar were added the appropriate radical precursor (1.2-1.5 equiv), the appropriate cyclopropane linchpin (0.3 mmol, 1 equiv) and 4CzIPN (0.0118 g, 0.0150 mmol, 5 mol %). The vial was sealed with a cap containing a TFE-lined silicone septa and placed under an N_2 atmosphere through evacuating and purging with N_2 three times via an inlet needle. The vial was then charged with degassed anhyd DMSO (6 mL) via a syringe The cap was sealed with Parafilm®, and the now bright-yellow soln was irradiated with blue LEDs in the a photoreactor. The temperature of the reaction was maintained at approximately 30 °C via fan cooling. The soln was stirred vigorously while being irradiated. After confirmation of reaction completion by HPLC/TLC (typically 3-16 h), the now dark (or in some cases clear) soln was transferred to a separatory funnel and diluted with Et_2O (~20 mL) and 2 M aq NaOH (~20 mL). The layers were separated, and the aq layer was extracted with additional Et_2O (2 × ~10 mL). The combined organic layers were washed with additional 2 M aq NaOH (2 × ~10 mL). The organic layer was then washed with deionized H_2O (2 × ~20 mL) followed by brine (~25 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed *in vacuo* by rotary evaporation. Further purification was accomplished by SiO_2 column chromatography (typically eluting with hexanes/EtOAc or hexanes/Et_2O).

Acknowledgements

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