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Chemoenzymatic Dynamic Kinetic Resolution of Secondary Alcohols and Amines Employing Copper-Based Photocatalysis

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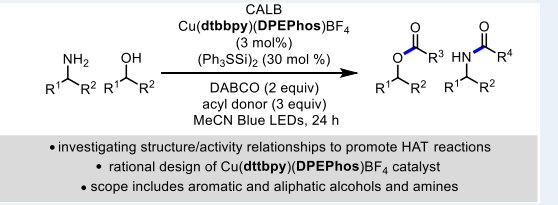
ABSTRACT: A tandem photo- and biocatalytic dynamic kinetic resolution of secondary alcohols and amines was achieved employing a commercially available lipase, *Candida antarctica* lipase B (CALB), and a heteroleptic copper complex. The process is an example of using copper-based photocatalysis to promote hydrogen atom transfer (HAT) processes employing thiyl radicals. Screening of 48 complexes and 5 disulfides identified Cu(dtbbpy)(DPEPhos)BF_4 and $(Ph_3SiS)_2$ as an optimal catalyst system to promote the HAT process. The catalytic system represents a general system for radical-mediated racemization applicable to both aliphatic and aromatic alcohols and amines (18 examples, 60 → 97% yield, 76 → 99% ee).



KEYWORDS: *copper, photocatalysis, dynamic kinetic resolution, secondary alcohols, biocatalysis*

1. INTRODUCTION

Photocatalysis[1] and biocatalysis[2] are both regarded as green tools for molecular synthesis that proceed under relatively mild reaction conditions. It is not surprising that the merger of the two fields has garnered significant interest. Where photocatalysis can be exploited to promote redox transformations or generate reactive intermediates, biocatalysis is utilized to perform asymmetric synthesis with often exquisite levels of selectivity. Photo-biocatalysis can involve enzymes that require light for catalytic activity and take advantage of the chiral environment to induce asymmetry.[3] Such processes can be used to address long-standing challenges in molecular synthesis, such as enantioselective C_{sp^3}−C_{sp^3} couplings.[4] Photo-biocatalysis can also utilize both individual enzymes and photocatalysts in linear cascades. Such systems often manipulate photocatalysis to engage challenging redox transformations, in tandem with a stereoselective enzymatic step, often, but not exclusively, with co-factors.[5] The coupling of biocatalysis and transition metal catalysis also provides powerful tools for molecular synthesis. The Bäckvall dynamic kinetic resolution of alcohols is a potent chemoenzymatic strategy for preparing enantioenriched secondary alcohols and amines from racemic precursors.[6] The process typically employs lipases and proteases as enantioselective acylating agents and transition metal complexes as catalysts to promote racemization of the secondary alcohol or amine. Different catalysts can promote racemization either through sequential oxidation/reduction[7] or via reversible carbocation formation.[8]

In 1998, Roberts studied an alternative mechanism for racemization via radical chain mechanisms employing thiyl radicals (Figure 1). Alkanethiols substituted by electron-withdrawing groups could racemize (*R*)-tetrahydrofurfuryl acetate,[9] and subsequent reports demonstrated that thiyl radicals could also epimerize 1,2-diols.[10] In 2006, Bertrand et al. showed that the same strategy could be employed for the racemization of non-activated aliphatic amines using thioglycolate/AIBN to thermally generate thiyl radicals.[11] Exploiting knowledge of important S−H and C−H bond dissociation energies (BDEs) for designing such processes, a dynamic kinetic resolution (DKR) process was later developed for aliphatic amines.[12]

Recently, photocatalysis has emerged as a mild and efficient route to hydrogen atom transfer chemistry via thiyl radicals. Wendlandt et al. reported that Ir-based photocatalysts under blue light irradiation promote selective, catalytic isomerization of *cis*-1,2-diols to *trans*-diequatorial-1,2-diols employing triphenylsilanethiol (Ph_3SiSH) as a co-catalyst.[13] The power of the strategy was particularly effective for selective "editing" of stereocenters in complex carbohydrates.[14] Other photocatalytic systems employing decatungstate complexes[15] and thermally promoted processes[16] have also been reported for selective isomerizations via hydrogen atom transfer (HAT) and many other thiyl-mediated HAT processes continue to be reported.[17] Not surprisingly, the first photocatalytic and enzymatic DKR for unactivated aliphatic amines was reported in 2018 by Zhou et al.[18] Using an Ir-based catalyst and *n*-OctSH, a variety of primary aliphatic amines were converted to

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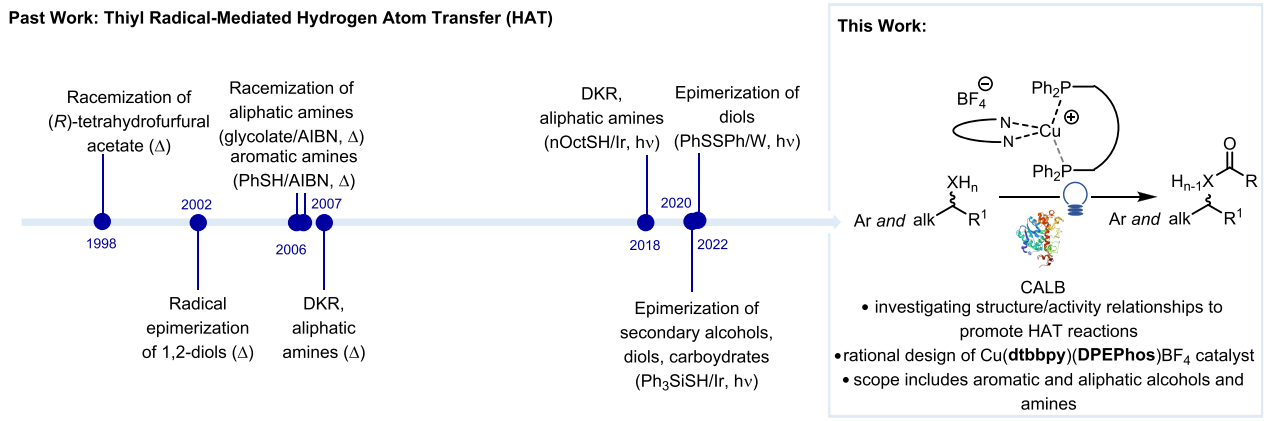

Figure 1. A timeline of thiyl-radical-promoted HAT/isomerization toward photocatalytic chemoenzymatic dynamic kinetic resolution.

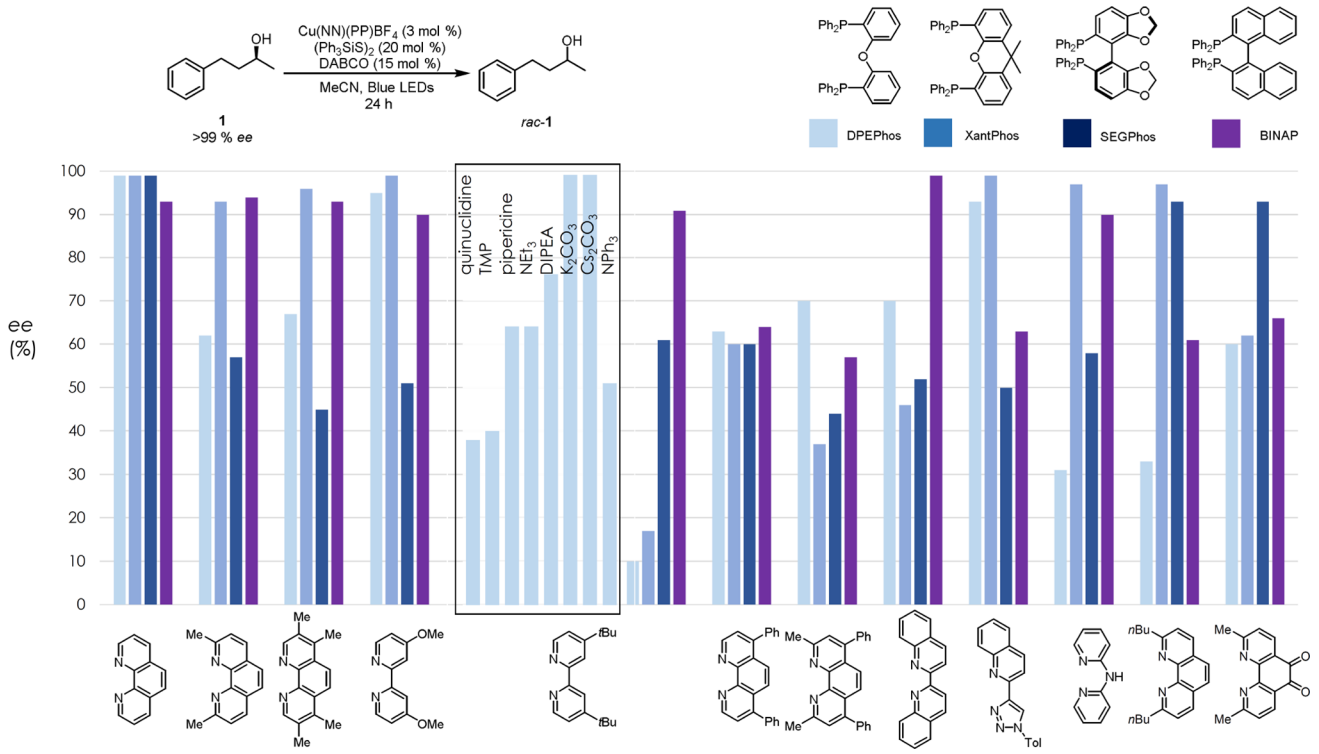

Figure 2. Optimization of a heteroleptic copper complex for racemization of secondary alcohols.

their corresponding amides in high yields and enantioselectivities. Despite the ability of photocatalysis to promote mild racemization of stereocenters, it is surprising that its compatibility with biocatalysis in the context of DKR has not been further developed. While radical-based approaches have been studied in the past two decades for aliphatic amines, extensions to aliphatic alcohols and more widely used aromatic substrates are noticeably absent, and investigation of alternative photocatalysts is still in its infancy. Our group has demonstrated that heteroleptic copper complexes[19,20] of the type Cu(NN)(PP)X can be fine-tuned for various applications in photocatalysis,[21,22] and it is probable that they could be designed for HAT-type processes. Herein, we report on the design of a heteroleptic copper-based complex for a photocatalytic and chemoenzymatic DKR of secondary alcohols and amines with broad scope.

2. RESULTS AND DISCUSSION

2.1. Optimization of the Catalyst System. To optimize a heteroleptic copper complex for HAT, a series of different diimine (NN) and bisphosphine (PP) ligands were selected for evaluation (Figure 2).

Four bisphosphines were selected: two bisphosphines with wide bite angles, DPEPhos and XantPhos, and two with smaller bite angles, SEGPhos and BINAP. Twelve diimine ligands were selected that had varied electronics, steric effects, and coordination geometry, leading to a total of 48 different catalyst structures. As a starting point, $(Ph_3SiS)_2$ was selected as a disulfide, given previous reports of the parent silane as an effective HAT promoter.[14] DABCO was chosen as an electron donor and acetonitrile as the solvent, and the reaction mixtures were irradiated under blue LEDs.[23] Efficiency was judged by the degree of racemization of secondary alcohol **1** over 24 h (Figure 2). In examining general trends, heteroleptic

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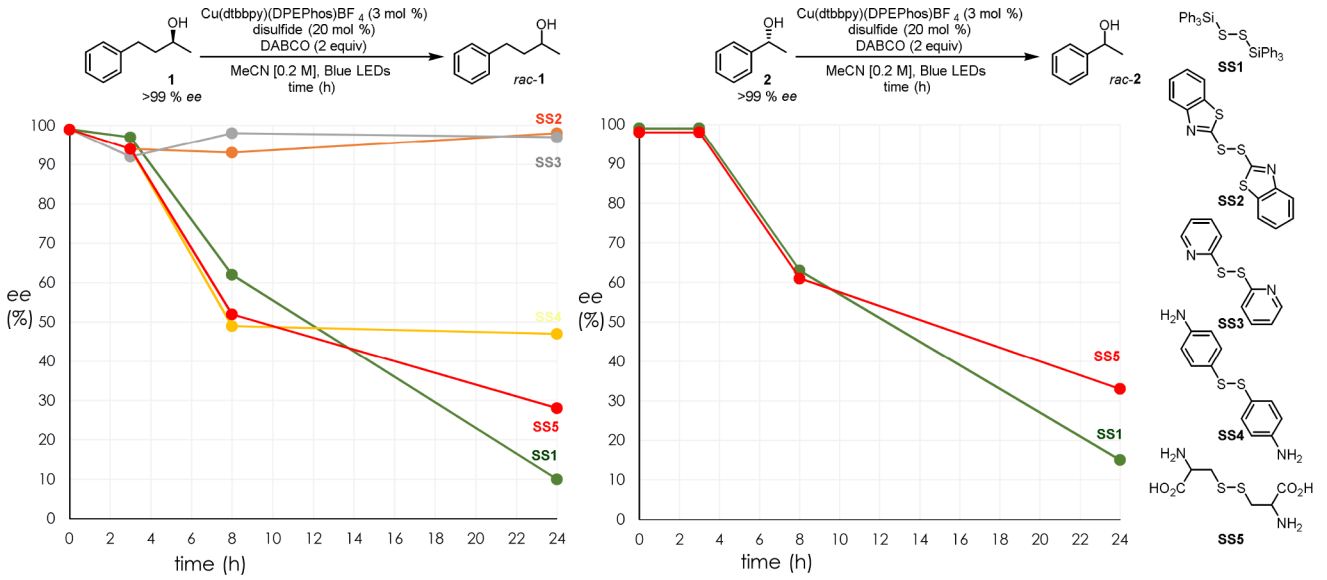

Figure 3. Optimization of the disulfide for the photocatalytic racemization of secondary alcohols.

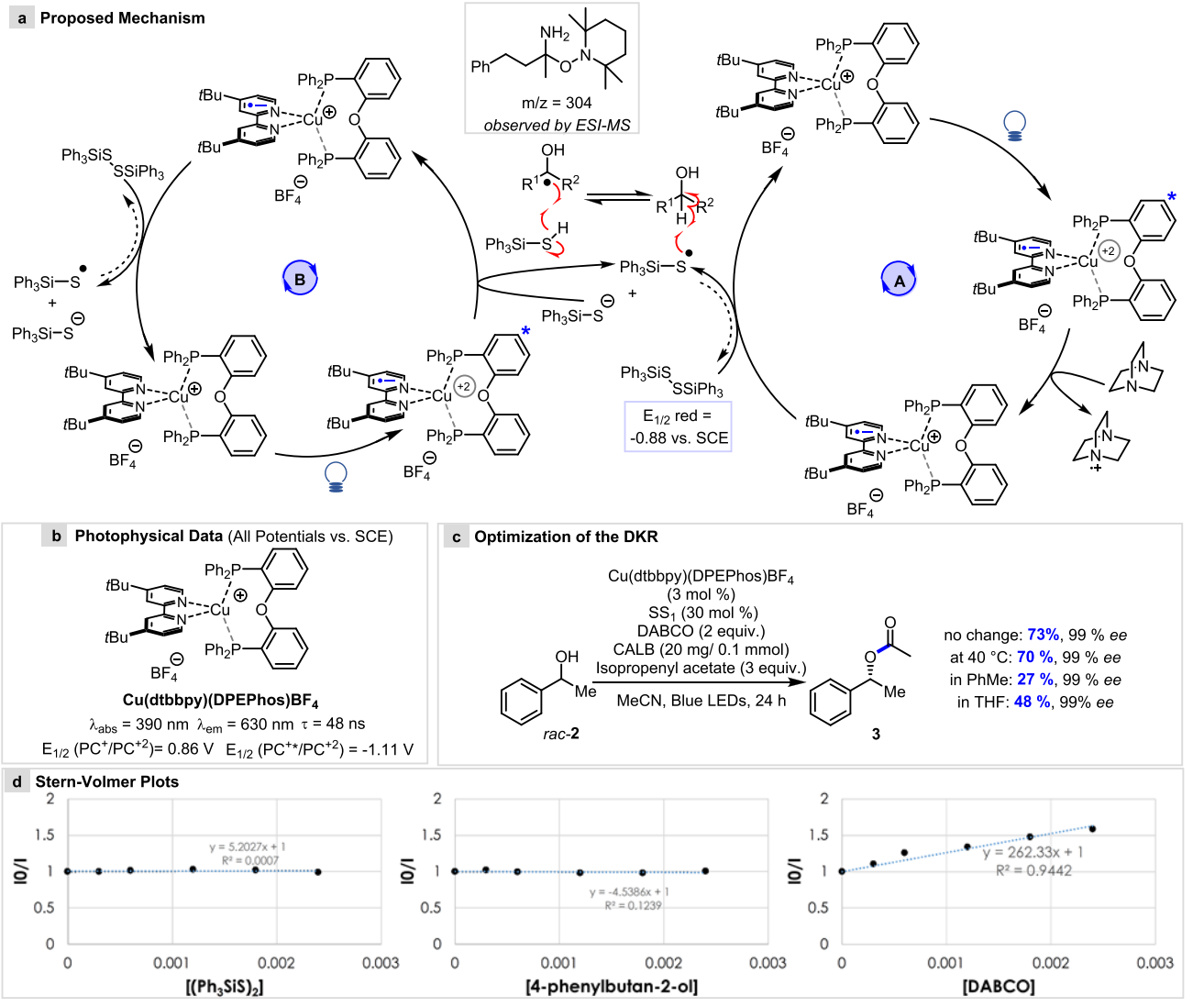

Figure 4. Proposed mechanism: (a) possible catalytic cycles, (b) catalyst photophysical data, (c) optimization of the resulting DKR of secondary alcohols, and (d) Stern–Volmer plots for the racemization reaction.

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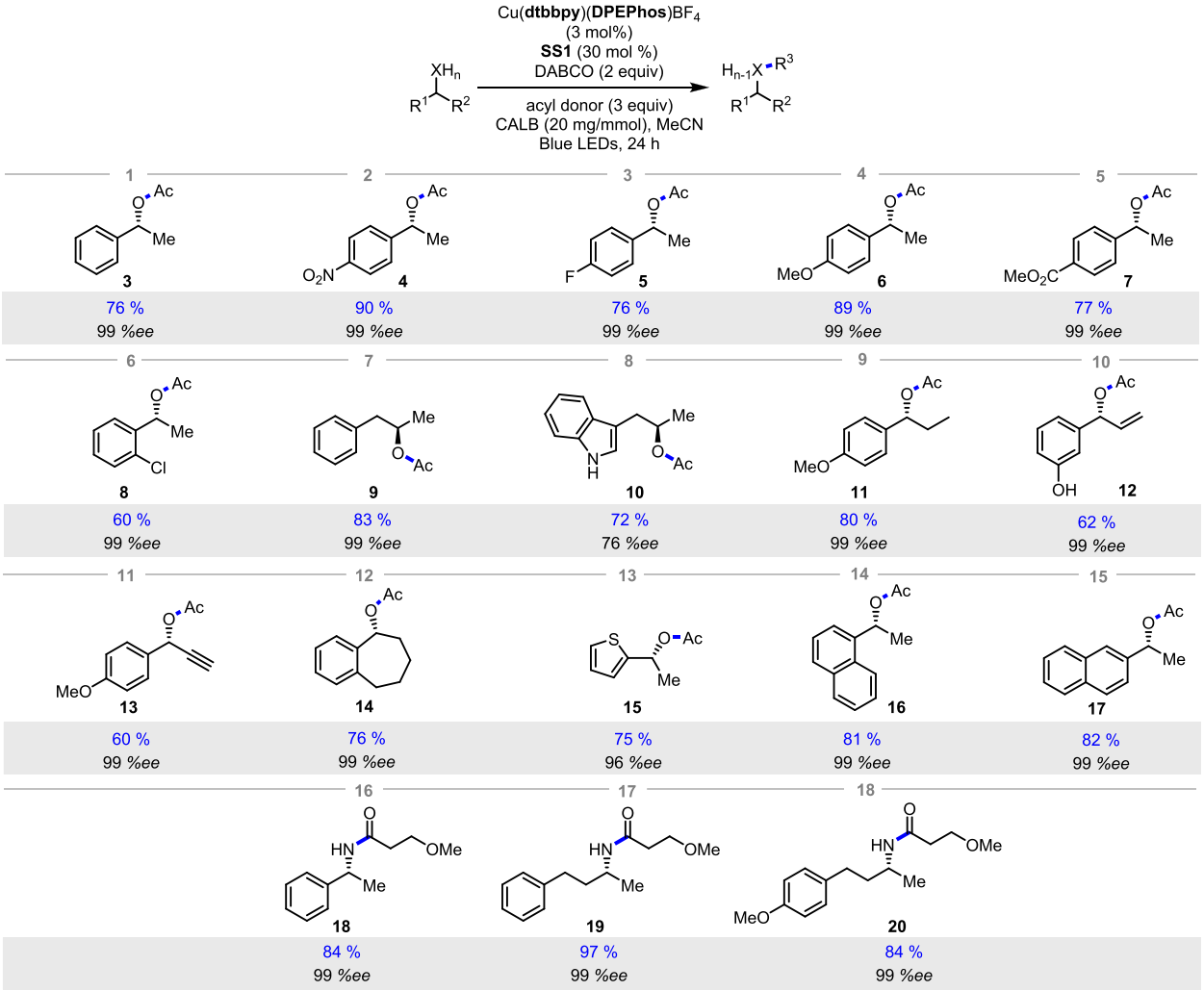
Table 1. Photochemical DKR of Secondary Alcohols and Amines Employing the Cu(dtbbpy)(DPEPhos)BF_4 Catalyst[a]



[a]Yields following chromatography.

complexes derived from SEGPhos tend to show good levels of racemization of **1** over 24 h (~<60% ee of **1**). Previous reports have suggested that bisphosphines with small bite angles tend to afford complexes that are good excited-state electron acceptors.[21] Among the diimines, four ligands (dtbbpy (4,4′-di-*tert*-butyl-2,2′-dipyridyl), batho (4,7-diphenyl-1,10-phenanthroline), bathocup (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline), dq (2,2′-biquinoline)) displayed generally good levels of racemization.

Several of the ligands have also been used in other heteroleptic copper complexes for single-electron transfer chemistry. Surprisingly, only two complexes afforded secondary alcohol **1** in less than 20% ee after 24 h, with the complex Cu(dtbbpy)(DPEPhos)BF_4 being the best (10% ee of **1**). The large-bite-angle DPEPhos is well-established to reinforce the tetrahedral geometry of the ground and excited states, enhancing the emissive properties of the complex. While in most cases, the absorption coefficient is lower compared to those of analogous homoleptic diimine complexes, excited-state reduction potentials remain similar, while oxidation potentials are much improved. The sum effect results in complexes that are both efficient reducing and oxidizing agents in their excited states.[19e] Subsequently, a survey of different bases to replace DABCO was carried out (see inset in Figure 2); however, none was as effective as DABCO. Among the organic and inorganic bases selected, the inorganic bases were largely unproductive, while others that could serve as good electron donors (quinuclidine, TMP, NPh_3) afforded some racemization of alcohol **1** (<50% ee). Note that when the racemization of secondary alcohol **1** with disulfide **SS1** was conducted in the dark, no racemization was observed either at room temperature (79% recovered **1**, 99% ee) or at 40 °C (70% **1**, 99% ee). Similarly, no racemization was observed in the absence of the copper catalyst (83% **1**, 99% ee).[24] When disulfide **SS1** was replaced by its corresponding thiol (Ph_3SiSH), the racemization process shut down.[25] Next, the effect of the nature of the disulfide was investigated. Five disulfides were selected, namely, the original $(Ph_3SiS)_2$ **SS1**; two with heteroaromatic substituents (**SS2** and **SS3**); one with aromatic substituents, **SS4** (BDE = 70 kcal/mol); and one with aliphatic substituents, **SS5** (BDE = 86 kcal/mol) (Figure 3).[26] The racemization of aliphatic secondary alcohol **1** was investigated at various time points over 24 h to gauge its reactivity (Figure 3, left). The heteroaromatic-substituted disulfides did not produce almost any racemization over a 24 h period. The racemization of alcohol **1** plateaued at approximately 50% ee with aromatic disulfide **SS3**. Encouraging results were obtained with the dicysteine derivative **SS5**,

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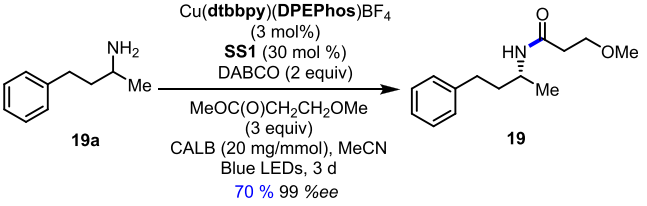
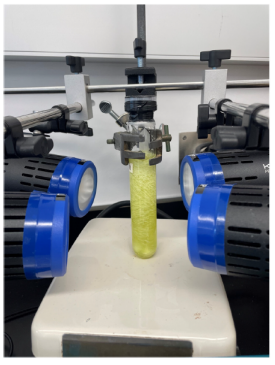
arriving at 33% ee of **1** after 24 h. Despite the encouraging reactivity, **SS1** remained the most active. Both **SS1** and **SS5** were then investigated in the racemization of benzylic alcohol **2** (Figure 3, right). Gratifyingly, both **SS5** and **SS1** again produced good levels of racemization of the benzylic alcohol, with **SS1** affording the lowest ee after 24 h (15% ee of **2**).

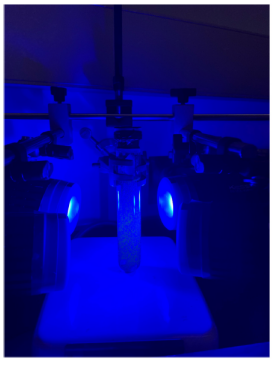
The racemization of the secondary alcohols is proposed to occur via HAT with a thiyl radical. There are several possibilities for generating thiyl radicals (Figure 4a). Upon irradiation with blue LEDs, Cu(dtbbpy)(DPEPhos)BF_4 is promoted to its excited state. A report from Glorius et al. suggested that disulfides can undergo transformation to thiyl radicals via an energy-transfer mechanism.[27] Stern−Volmer plots display no quenching with disulfide **SS1**, or a secondary alcohol, but rather with the DABCO additive. One possibility is that following reductive quenching, subsequent SET from the reduced ground state of Cu(dtbbpy)(DPEPhos)BF_4 to **SS1** generates the thiyl radical (catalytic cycle A, Figure 4a). While some disulfides are reduced at low potentials (∼1.6 to −2.8 V),[28] the cyclic voltammograms of **SS1** showed a much lower reduction potential ($E_{1/2}$ red = −0.88 V vs SCE). If such reduction were to occur, the thiyl radical could undergo productive reversible HAT to racemize the secondary alcohol. TEMPO trapping of a radical intermediate for a secondary amine substrate was observed via ESI−MS analysis. As no racemization is observed when the corresponding thiol is used in place of the disulfide, this suggests that some mechanism is operative to generate thiyl radicals from the disulfide. Reduction of the disulfide would also result in the formation of the thiolate anion. Such thiolates are good single-electron reducing agents and could also quench the excited state of the copper complex in an alternate catalytic cycle (catalytic cycle B, Figure 4a). In doing so, another equivalent of the thiyl radical would be generated for HAT with the secondary alcohol. With conditions in hand for photochemical racemization, a DKR process was investigated using racemic secondary alcohol **2**, solid-supported *Candida antarctica* lipase B (CALB), and isopropenyl acetate as the acyl donor (Figure 4c). Experimentation revealed that **2** could be converted to (*R*)-**3** at 73% yield and 99% ee after 24 h. Heating the reaction to 40 °C to promote enzyme activity had no significant effect on the outcome of the DKR. Repeating the DKR in either PhMe or THF resulted in a significant drop in the yield of (*R*)-**3** (27−48% yield).

2.2. Evaluation of Scope. Following identification of the Cu(dtbbpy)(DPEPhos)BF_4/$(Ph_3SiS)_2$ (**SS1**) catalytic system, it was evaluated in the biocatalytic/photocatalytic DKR of various alcohols and amines (Table 1). As model secondary alcohol **2** underwent DKR to afford acetate (*R*)-**3** at 76% isolated yield (99% ee), further evaluation of the tolerance to aromatic substituents was probed. Nitro-substituted acetate **4** was isolated at 90% yield (99% ee), demonstrating that the nitro substituent did not interfere with the photochemistry. Furthermore, the presence of *p*-fluoride (**5**), *p*-methoxy (**6**), *p*-methylcarboxy (**7**), or *o*-chloride (**8**) all afforded the corresponding acetates in good yields and enantioselectivities (60 → 89%, 99% ee). Unactivated aliphatic alcohols were equally reactive: acetate **9** was isolated at 99% ee, while indole-based acetate **10** was isolated at 76% ee.[29] Secondary alcohols bearing substituents other than Me that are accepted by CALB were also well tolerated (**11** → **13**). In particular, the successful DKR to afford alkenyl-substituted **12** and alkynyl-substituted **13** are noteworthy. During DKR, the α-substituted radical intermediates could undergo delocalization with the alkene or alkyne to afford rearranged products. However, acceptable yields and ee's were obtained for all substrates. Secondary alcohols with other aromatics, such as 1-benzosuberyl, 2-thiophenyl, 1-naphthyl, or 2-naphthyl, were also all well tolerated in the biocatalytic/photocatalytic protocol (**14** → **17**, 75 → 82%, 96−99% ee). Finally, secondary amines were also subjected to DKR (Table 1, entries 16−18). Amide **18** was isolated at 84% yield and 99% ee. It should be noted that in previous attempts at racemization using thermal conditions (PhSH, AIBN, Δ),[30] low yields of the racemized amine (30−50%) were obtained as competing oxidation and imine formation were observed. Unactivated amines afforded amides **19** and **20** at high yields and enantioselectivities as well and were used to demonstrate the DKR on a larger scale. Amine **19a** was subjected to the optimized conditions for a reaction time of 3 days (Scheme 1) and afforded amide **19** at 70% (99% ee).

Scheme 1. Gram-Scale Synthesis via DKR







In summary, a tandem photo- and biocatalytic DKR of secondary alcohols and amines was achieved employing a commercially available lipase and a heteroleptic copper complex. The racemization was made possible by a Cu(NN)(PP)X-type complex, an example of using copper-based photocatalysis to promote HAT processes employing common thiyl radicals. A screening approach identified Cu(dtbbpy)(DPEPhos)BF_4 from among 48 complexes, and $(Ph_3SiS)_2$ from among five disulfides, as an optimal catalyst system to promote the HAT process. In contrast to previous radical-mediated racemization methods (thermal and photochemical), the catalytic system described herein is the first general system applicable to aliphatic and aromatic alcohols and amines (18 examples, 60 → 97% yield, 76 → 99% ee). The above exemplifies the potential utility to exploit photocatalysis using base metal complexes in modern HAT processes and synthesis mediated by thiyl radicals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c01713.

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Experimental procedures and characterization data, development of racemization, tabular data from screening, substrate synthesis, DKR procedures and experimental data, absorbance and emission data, excited-state lifetime data, Stern−Volmer experiments, electrochemical data, TEMPO experiments, NMR data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(25) When the racemization of **1** was conducted under optimized conditions with Cu(bathocup)(XantPhos)BF_4 (2 mol %), DABCO (10 mol %) and $(Ph_3SiS)_2$ (30 mol %), MeCN, blue LEDs, 18 h, a 37% ee of **1** was observed. When $(Ph_3SiS)_2$ was exchanged for Ph_3SiSH (30 mol %), the ee of recovered **1** was 99%.
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