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Enantioselective β-Protonation of Enals via a Shuttling Strategy

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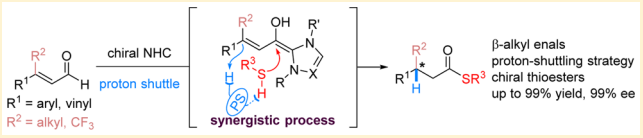
Supporting Information

ABSTRACT: Remote asymmetric protonation is a long-standing challenge due to the small size of protons. Reactions involving electron-deficient olefins pose a further difficulty due to the electrophilic nature of these substrates. We report a shuttling system that delivers a proton in a highly enantioselective manner to the β-carbon of enals using a chiral N-heterocyclic carbene (NHC) catalyst. Choices of a Brønsted base shuttle and a Brønsted acid cocatalyst are critical for highly stereoselective β-protonation of the homoenolate intermediate and regeneration of the NHC catalyst results in functionalization of the carbonyl group. Thioesters with a β-chiral center were prepared in a redox-neutral transformation with an excellent yield and ee.



INTRODUCTION

Carbonyl compounds with a chiral center at the β-position are important building blocks in synthetic chemistry. These structural motifs are generally prepared by nucleophilic addition to readily available α,β-unsaturated carbonyl substrates. Representative examples include asymmetric Michael additions[1] and hydrogenations.[2] Reactions of this sort are carried out using stoichiometric reductive organometallic or organohydride species such as Zn,[1a,d] B,[1b] Mg,[1c] Si,[1e] Al,[1f] metal hydride,[2a−f] and Hantzsch esters.[2g−j] Protection against moisture and oxidative environments is often necessary. The carbonyl moiety, most commonly an aldehyde, ketone, amide, or ester, remains unchanged after the reaction. An alternative redox-neutral strategy that creates such chiral centers with concurrent transformation of the carbonyl group is highly step- and atom-economical.

N-heterocyclic carbenes (NHCs) are versatile catalysts that deliver *umpolung* activation of carbonyl groups and its conjugated double bond.[3] The biomimetic acyl anion mechanism via homoenolate intermediates is well-established for concomitant functionalization of a carbonyl group and its β-carbon (Figure 1).[4] NHCs react with an α,β-unsaturated aldehyde to generate an *umpolung* homoenolate intermediate which is nucleophilic at the β-carbon and electrophilic at the carbonyl center. This species can undergo double functionalization using a combination of a nucleophile and an electrophile. To date, asymmetric transformations involving this strategy have been applied mostly in cycloadditions (for example, the head-to-tail cycloaddition between a homoenolate and a dipolar reagent).[5] In fact, a nucleophile alone can add across the β-carbon and carbonyl center of a homoenolate by providing an electrophilic proton. However, asymmetric noncycloaddition reactions involving nucleophiles are very rare.[6] The reason for this is the challenge which lies in the control of facial selectivity during protonation of the β-carbon of the homoenolate.[7] The proton is the smallest electrophile, and shielding one prochiral face is far less effective for an incoming proton than for other electrophiles. Although asymmetric α-protonation of the NHC-derived acyl azolium has been reported,[8] remote β-protonation of homoenolates remains a significant challenge. In the only report on highly enantioselective β-protonation of enals with a β-ester directing group, Scheidt et al. found that bulky thioureas are an effective cocatalyst that enhances facial shielding of the β-carbon by forming hydrogen bonds with a β-ester group.[7e,g] This method not only stabilizes the corresponding homoenolate intermediate but also enhances chiral communication between the NHC and the β-carbon. In contrast, β-alkyl enals are notorious as substrates in asymmetric β-protonation. β-Methylcinnamaldehyde, for example, lacks a β-directing group and leads to poor selectivity (53% ee).[7c,d] This type of substrate is prone to *E*/*Z* isomerization, further complicating the stereoselectivity issue. In this paper, we report our serendipitous discovery of a simple shuttling strategy that delivers highly enantioselective β-protonation of enals in the absence of any directing group.

To solve the longstanding challenge of enantioselective enal β-protonation, we initially proposed a tethered catalyst strategy. We envisioned that a Lewis acid cocatalyst might bridge chirality transfer from an NHC to the distal β-carbon (Figure 2).[5c,j,9] In this scenario, the enol functionality might serve as an internal directing group by coordinating to a Lewis acid which, in a cyclic transition state, might guide protonation to occur from only one face. A common competing side reaction involving homoenolate is oxidation to vinyl acyl azolium.[5h,7d,10] Tethering the enol and thiol not only might stabilize a homoenolate intermediate but also could accelerate protonation by enhancing the acidity of the thiol.

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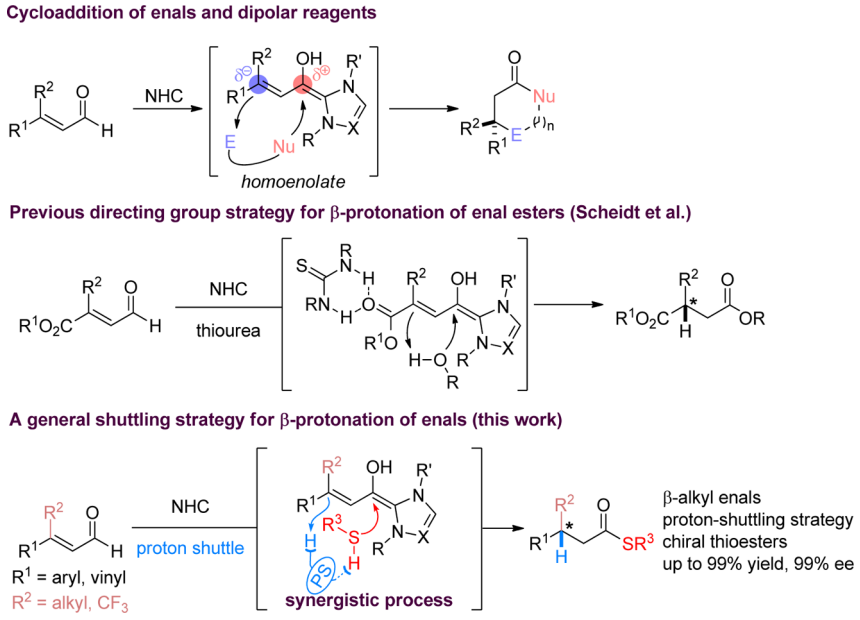


Figure 1. Construction of the β-chiral center of carbonyl compounds.

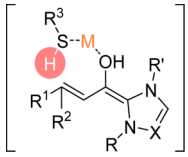
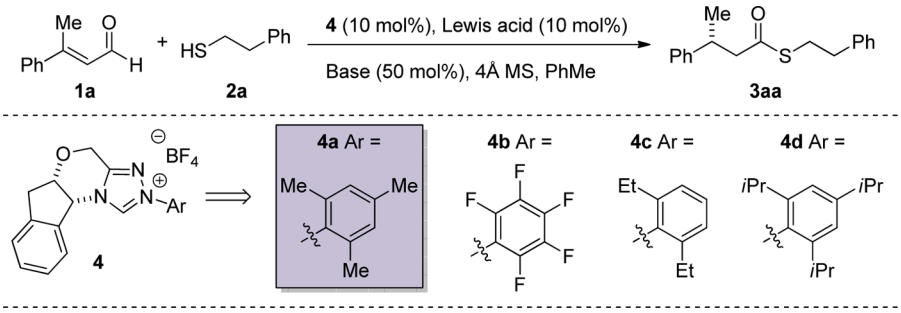


Figure 2. Original model of synergistic catalysis using NHC/Lewis acid.

RESULTS AND DISCUSSION

To test our design, we used β-methyl cinnamaldehyde (**1a**) and 2-phenylethanethiol (**2a**) as model substrates. The reaction using the catalytic NHC precursor (**4a**) and DABCO resulted in a 53% yield and 67% ee (Table 1, entry 1). Use of 4 Å molecular sieves slightly improved the yield. We found that introduction of various Lewis acids has a strong impact on the enantioselectivity. Mg[9a] and Sc[9d] compounds gave only

Table 1. Optimization of Conditions[a]



entry	NHC cat.	Lewis acid	base	yield[b] (%)	ee[c] (%)
1	**4a**	–	DABCO	53	67
2	**4a**	$Mg(OTf)_2$	DABCO	42	70
3	**4a**	$Sc(OTf)_2$	DABCO	24	74
4	**4a**	$Zn(OTf)_2$	DABCO	92	94
5	**4a**	$Cu(OTf)_2$	DABCO	96	95
6	**4a**	$Cu(OTf)_2$	quinulidine	81	95
7	**4a**	$Cu(OTf)_2$	DMAP	65	52
8	**4a**	$Cu(OTf)_2$	DBU	31	36
9	**4a**	$Cu(OTf)_2$	DIPEA	39	15
10	**4a**	$Cu(OTf)_2$	K_2CO_3	trace	n.d.
11	**4b**	$Cu(OTf)_2$	DABCO	59	79
12	**4c**	$Cu(OTf)_2$	DABCO	57	97
13	**4d**	$Cu(OTf)_2$	DABCO	38	80
14[d]	**4a**	$Cu(OTf)_2$	DABCO	83	95

[a]Reactions were performed using 0.1 mmol of **1a** and 0.12 mmol of **2a** in 1.0 mL of toluene at rt for 5 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]5 mol % **4a** and Lewis acid.

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yields and selectivity (**Figure 3**, product **3ab-3ae**).

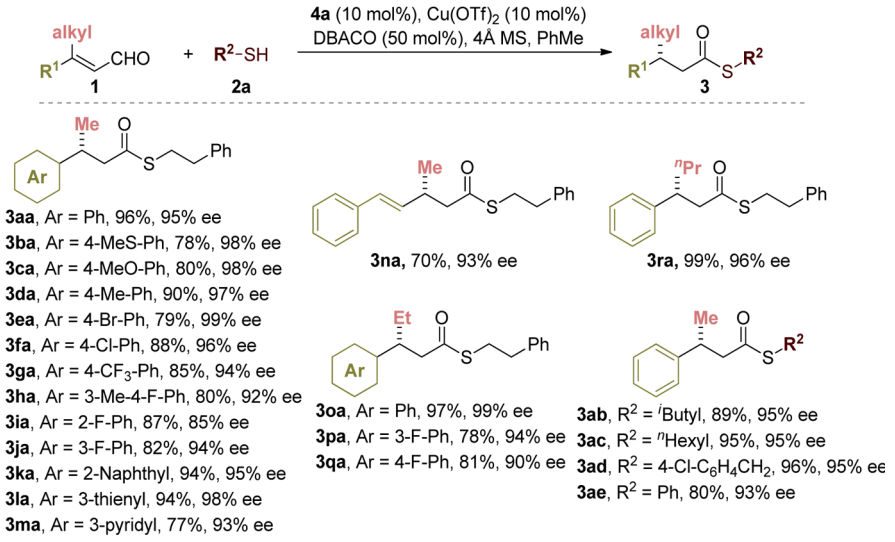

Figure 3. Substrate scope of β-disubstituted enals.

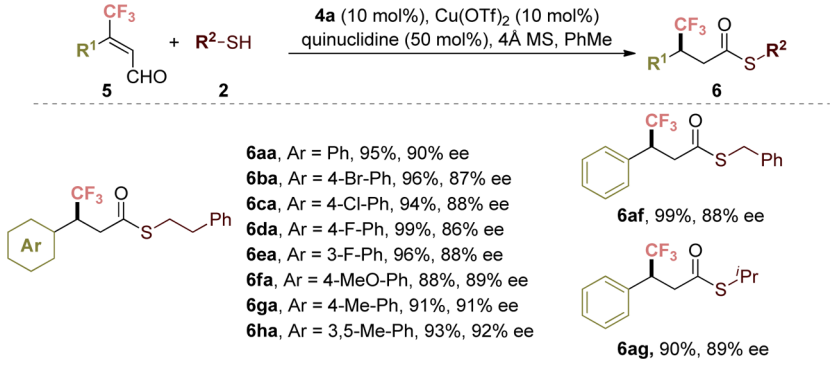

Figure 4. Substrate scope for β-CF_3 enals.

marginal improvement (entries 2 and 3), and both Zn and Cu compounds resulted in high yields and ee's (entries 4 and 5). These results suggest that the selectivity of this reaction is directly correlated with the sulfur binding affinity of metals.[11] Interestingly, the choice of base was found to be crucial for the enantioselectivity. Among the organic bases examined, only bridgehead nitrogen bases, i.e. DABCO and quinuclidine, delivered high ee's (entries 5 and 6). Acyl transfer catalysts, such as DMAP, failed to promote a faster and more selective protonation/thioesterification sequence. This result suggests that thiols are sufficiently nucleophilic to turnover the NHC catalyst by themselves (entry 7). Poor ee values were observed using DBU and Hünig's base (entries 8 and 9). Potassium carbonate did not give any desired product due to lack of a proton source in the reaction (entry 10). The structure of the NHC precursor (**4**) was briefly examined. The pentafluoroaryl substituted analogue (**4b**) gave poor conversion and ee, probably due to the reduced nucleophilicity of the corresponding homoenolate and a competing pathway for formation of an unsaturated ester (entry 11).[5h,7d] The reaction proceeded poorly when methyl groups on **4a** were replaced by bulky ethyl or isopropyl groups (catalyst **4c** and **4d**) (entries 12 and 13). The gradual decrease of conversion indicated that the formation of the homoenolate might be challenging in these cases since a large amount of start material remained.[12] Reducing the loading of both catalysts to 5 mol % did not affect the ee (entry 14). A combination of **4a** and $Cu(OTf)_2$ was chosen as the optimal catalyst system. Although the NHC/Cu(I) system has been reported by Chi and co-workers,[13] this work represents the first report of NHC/Cu(II) synergistic catalysis.

The scope of the enal was investigated using the aforementioned reaction conditions (Figure 3). Electron-rich and electron-poor substituents at various positions are well tolerated by the β-aryl group (product **3aa**−**3ja**). Challenging substrates with an *ortho*-substituent performed well (product **3ia** for example). Substrates with a β-thienyl group gave a 94% yield and 98% ee. Remarkably, a basic β-pyridyl group did not interfere with either the Lewis acid or protonation. The dienal (**1n**) yielded the β-protonation product in 70% yield with 94% ee and exclusive regioselectivity (product **3na**). Besides methyl, enals with higher order β-alkyl groups were equally effective and selective (**3oa**−**3ra**) but β-dialkyl enals failed to react under these reaction conditions, due to unproductive homoenolate formation. Simple alkyl mercaptans and more acidic derivatives were evaluated and afforded comparable yields and selectivity (Figure 3, product **3ab**−**3ae**).

Trifluoromethylated chiral centers are particularly attractive in medicinal chemistry, but such products are challenging in asymmetric hydrogenation and Michael addition reactions. The orchestration of NHC/$Cu(OTf)_2$ cooperative catalysis is effective for enantioselective β-protonation of enals with a β-

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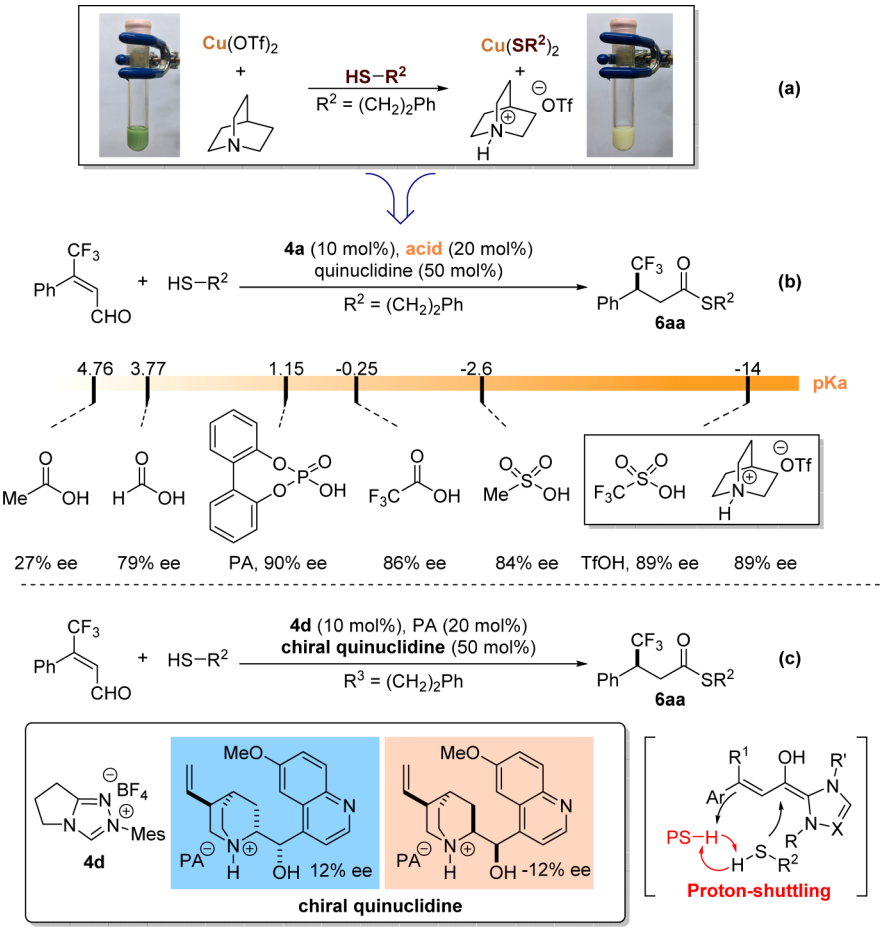

Figure 5. A shuttling mechanism for asymmetric β-protonation.

CF_3 group. Switching from DABCO to quinuclidine delivers better enantioselectivity (Figure 4). The reaction exhibits a similar substituent effect on the β-aryl moiety (Figure 4, product **6ba**–**6ha**). Both high yields and high ee's are obtained when benzyl mercaptan and isopropyl mercaptan are used as nucleophiles (Figure 4, product **6af**, **6ag**). The β-aryl was essential for high enantioselectivity under the standard conditions. No reaction occurred for β-dialkyl enals.

During these preliminary studies, we observed an interesting experimental phenomenon which suggests an alternative mode of asymmetric control in our proposed NHC/Lewis acid cooperative mechanism. A mixure of $Cu(OTf)_2$, precatalyst (**4a**), quinuclidine, and 4 Å molecular sieves in toluene is a bright green suspension which changes to pale yellow immediately upon addition of mercaptan. This observation suggests rapid formation of copper sulfide and quinuclidinium triflate (Figure 5a).[14] The quinuclidinium ion is a stronger acid than mercaptan (RN_3^+–H, pK_a = 9.8 vs RS–H, $pK_a \approx 15$, DMSO) and may well be the actual proton source rather than mercaptan. This hypothesis is supported by data in Table 1, where the structure of the base is essential for enantioselectivity. If quinuclidinium triflate is the actual proton source, there would be little interaction between copper and the homoenolate. In other words, copper would play no part in the key protonation step. The role of copper is to generate the quinuclidinium ion, a more effective and selective proton source, from quinuclidine and mercaptan.

Entry 1 in Table 1 shows that the mercaptan (**2a**) reacts with the enal (**1a**) in the absence of any Lewis acid, giving a moderate ee. This indicates that mercaptan itself is a nonselective proton source. Quinuclidine did not react with the thiol due to the large pK_a gap. In order to verify this finding, we examined reactions replacing $Cu(OTf)_2$ with various Brønsted acids by forming quinuclidinium in situ (Figure 5b). We were delighted to find that an acid cocatalyst can effectively promote the reaction. Weaker acids are in equilibrium with quinuclidine, and the free acid acts as a parallel, nonselective proton source. In the case of strong acids, nearly all protons exist in the quinuclidinium form, which is a more reactive and selective proton source. High enantioselectivity was obtained when strong acids ($pK_a < 1$) were used. Identical yields and ee's were obtained using either preformed quinuclidine triflate or triflic acid.

Chiral quinuclidines, in combination with an achiral NHC (**4d**), were tested. Quinine and quinidine delivered 12% and −12% ee respectively (Figure 5c). The opposite facial preference further supports quinuclidinium as the proton source. When quinine and quinidine were used in conjunction with chiral NHC (**4a**), no match/mismatch was observed, suggesting the NHC is the primary selectivity modulator and the effect of the amine is mostly steric. Based on these results, it is evident that quinuclidine is a unique proton shuttle. The chiral influence of the NHC is well received by the bridgehead structure of quinuclidine.

The substrate scopes of enal and mercaptan were examined using the new organocatalytic protocol. Thioesters with a β-chiral center were prepared in excellent yield and with high ee (Figure 6). Heterocycles or functional groups that previously

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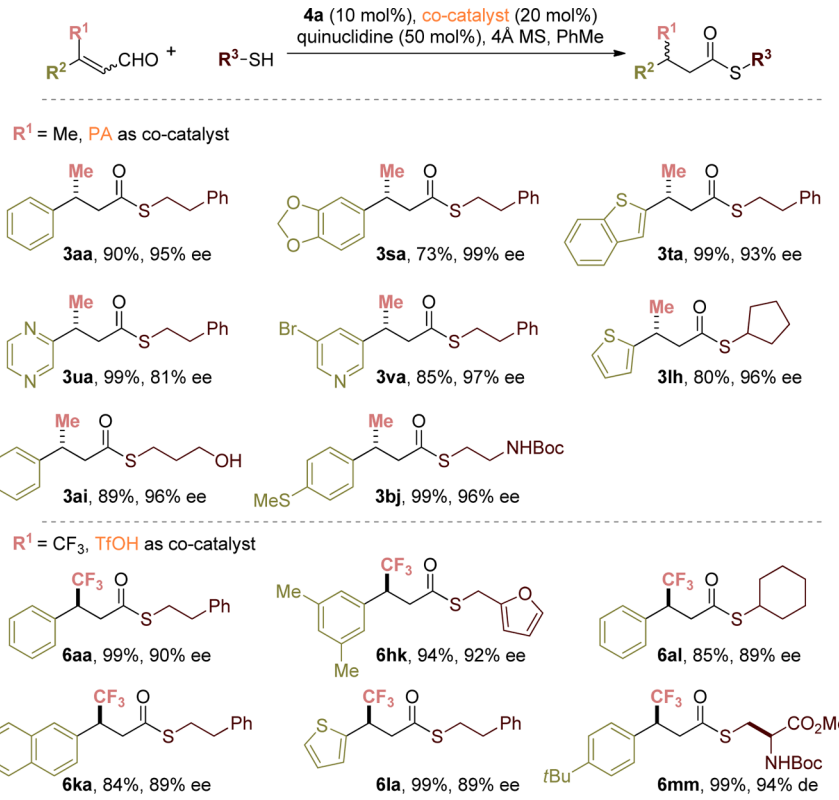

Figure 6. Expansion of substrate scope using the proton-shuttling strategy.

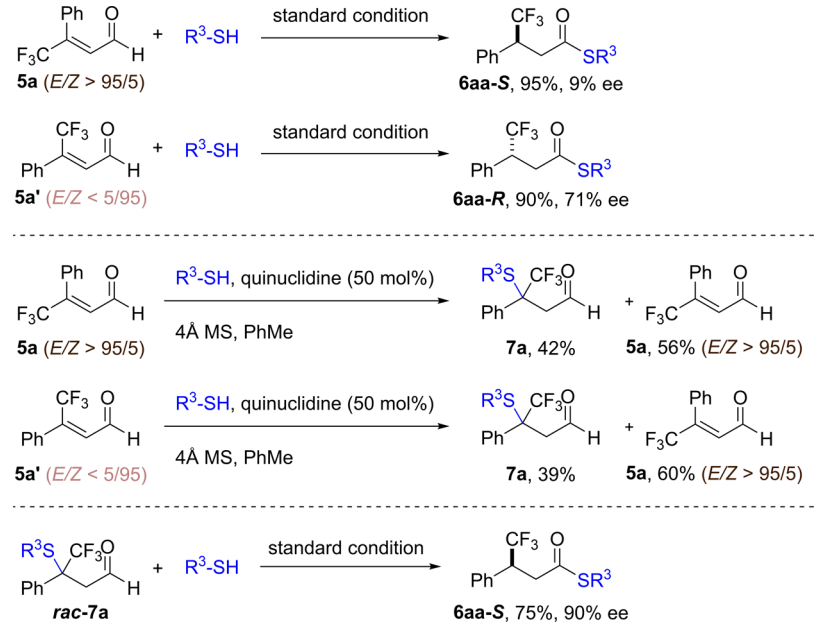

Figure 7. Mechanistic experiments.

were incompatible with the $Cu(OTf)_2$ conditions were well tolerated. For example, a β-pyrazinyl enal afforded the racemic product (**3ua**) in low yield using $Cu(OTf)_2$. Under the proton-shuttling conditions, **3ua** was isolated in 99% yield and 81% ee. In addition, mercaptans containing heteroatom substituents, which are poor substrates for the NHC/Cu(II) system, participate in β-protonation/thioesterification with excellent reactivity and selectivity under the organocatalytic conditions (**3ai**, **3bj**). Bulky secondary alkyl mercaptans showed no attenuation of reactivity under the standard conditions (**3lh**, **6al**). N-protected L-cysteine also functions as a valid thiol nucleophile, the corresponding product (**6mm**) being obtained in 99% yield and 97:3 de. The choice of acid also impacts the ee. Phosphoric acid (PA) generally affords a higher ee than TfOH for β-alkyl enals, while TfOH is more selective for β-CF_3 substrates (e.g., **3ua**, racemic product using TfOH vs 81% ee using PA; **6la**, 89% ee with TfOH vs 80% ee with PA).

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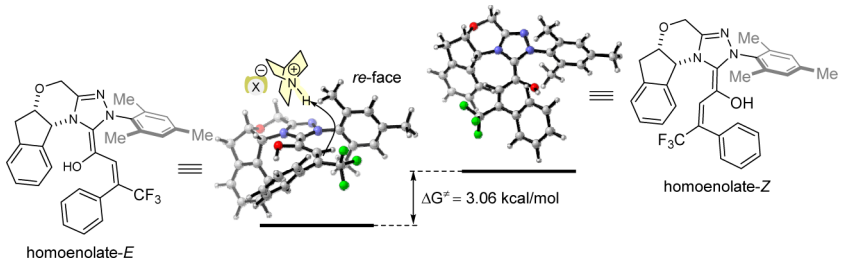

Figure 8. Minimized conformations of the homoenolate intermediate.

β-Trifluoromethyl and *β*-methyl enals generated a *β*-chiral center with an *S*[15a] and *R*[15b] configuration, respectively. This outcome is probably a result of the olefin geometry. *β*-Methyl enals are formed with a *trans* orientation of the carbonyl and *β*-aryl groups (*E* isomer), while *β*-CF_3 enals prefer to exist with a *cis* alignment of the carbonyl and *β*-aryl groups (*E* isomer). The independently prepared *Z* isomer of **5a** was subjected to the proton-shuttling reaction conditions, and the desired *β*-protonation product was obtained in 71% ee with the *R* configuration (Figure 7). *In situ* olefin isomerization of enal (**5a**) was examined, and proton shuttling conditions do not promote *E*/*Z* isomerization. However, this substrate suffered reversible sulfa-Michael addition when treated with mercaptan and quinuclidine. Both *E* and *Z* isomers of **5a** reacted with thiol (**3a**) at comparable rates. When **5a**-*Z* was used as the substrate, only its corresponding *E* isomer remained. These data suggest *β*-protonation of both geometric isomers of **5a** is equally efficient, and the *Z* form undergoes partial isomerization before the protonation is complete, resulting in the compromised ee for product **6aa**. When racemic sulfa-Michael adduct (**7a**) was subjected to the proton-shuttling conditions, product **6aa**-*S* was obtained in 75% yield and 90% ee. Retro-sulfa-Michael followed by enantioselective *β*-protonation is responsible for this outcome.

Facial differentiation in this transformation is most likely determined by the homoenolate intermediate with the lowest energy. Theoretical studies by Yates et al. suggest that Breslow enolates derived from triazolium precursors prefer to adopt the *E* conformation, in which the OH group is oriented away from the two adjacent nitrogen atoms.[16] A similar conclusion was obtained by minimization of the homoenolate from catalyst **4a** and enal **5a**. The B3LYP-D3/6-311+G** program determined that the *E*-conformer is 3.06 kcal/mol more stable than the *Z*-conformer. One of the *ortho*-methyl groups on **4a** shields the bottom *si*-face of homoenolate-*E*, leaving the top *re*-face open for the bulky proton shuttle (Figure 8). A similar rationale can be made for *β*-alkyl enals.

CONCLUSION

In summary, we have discovered a highly enantioselective *β*-protonation of enals using mercaptans via synergistic NHC/amine/copper catalysis. The high correlation between stereoselectivity and the sulfurphilicity of the metals led to identification of an organocatalytic proton-shuttling approach for highly stereoselective protonation of homoenolates. The combination of a bridgehead tertiary amine and a strong Brønsted acid cocatalyst was found to activate a crucial proton shuttle that delivers excellent reactivity and enantioselectivity. This strategy might find general applications in controlling *β*-chiral centers of carbonyl compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02889.

Experimental procedures, product characterizations, and copies of all NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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