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Reductive N-Heterocyclic Carbene Catalysis via Hydride Transfer: Generating Homoenolates from Unsaturated Esters

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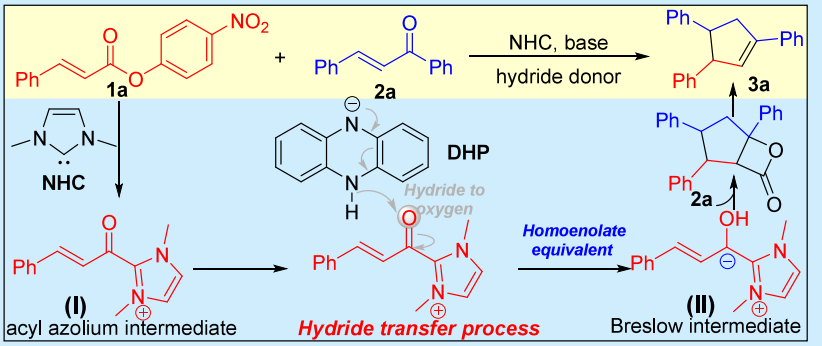

ABSTRACT: In N-heterocyclic carbene (NHC) catalysis, the reduction of NHC-bound acyl azolium species is achieved with progress limited to the generation of ketyl radical intermediates. Here, we report a novel NHC-catalyzed reductive mode for acyl azolium intermediates, which accept a hydride to generate the Breslow intermediate. Then, the reaction of the Breslow intermediate with chalcone results in the formation of cyclopentene, demonstrating a classic umpolung transformation. We expect that this catalytic reductive mode will open new avenues for synthetic transformations.

Reduction is a basic transformation in chemical and biological processes with enormous applications at various scales.[1−5] For instance, the Old Yellow Enzyme (OYE) family,[6−10] a class of flavin-dependent redox enzymes, has found extensive industrial uses for the reduction of activated alkenes.[11−13] In 1995, Massey[14] reported that OYE ene-reductases reduce activated alkenes.[15−19] In this process, β-nicotinamide adenine dinucleotide phosphate (NADPH)[20−22] serves as both a cofactor and a reductant, transferring a hydride during the reaction. More recently, Gruber[23] and Kroutil[24] reported the reduction of imines to their corresponding amines using NADPH. Their theoretical calculations revealed an unusual hydride transfer mechanism for imines bearing electron-withdrawing groups, such as ketones and carboxylic esters. Notably, they found that the N-terminus of the imine moiety is more electrophilic than the C-terminus, and this electrophilic N-terminus acts as the hydride acceptor during the enzymatic reduction.[25] Paul and co-workers later reported the reduction of α,β-dicarbonyl compounds by OYEs and NADPH, in which the carbonyl oxygen is proposed to act as the electrophilic site, accepting a hydride from NADPH (Figure 1a),[26] which is very similar to Gruber's findings.[25] These enzymatic reactions suggest an unusual umpolung reduction of activated imines and carbonyl compounds, providing valuable inspiration for the development of new catalytic chemical transformations.

Our interests in this direction were drawn to the design of N-heterocyclic carbene (NHC) organic catalysis for uncommon transformations.[27−31] In this arena, the oxidation of NHC-bound Breslow intermediates to the corresponding acyl azolium[32−36] or ketyl radical intermediates[37−40] has been well established (Figure 1b). In contrast, the reduction of NHC catalyst-bound intermediates (e.g., acyl azolium intermediates) is much less studied, and the limited success in these reductive NHC catalyses only correspond to ketyl radical intermediates for further single-electron-transfer reactions (Figure 1b).[41−46] Inspired by enzymatic reactions[22,47−49] and earlier NHC-mediated oxidative transformations,[30,40,50,51] here, we disclose that the acyl azolium intermediate can act as a weak oxidant to accept a hydride from a suitable reductant (Figure 1c). The key process is believed to involve a hydride transfer to the oxygen atom of the acyl azolium carbonyl, mimicking the OYE/NAD(P)H enzymatic process. In the process, 5,10-dihydro-phenazine (DHP) was used as a $FMNH_2$-type[52−54] reductant to reduce the acyl azolium intermediate. Notably,

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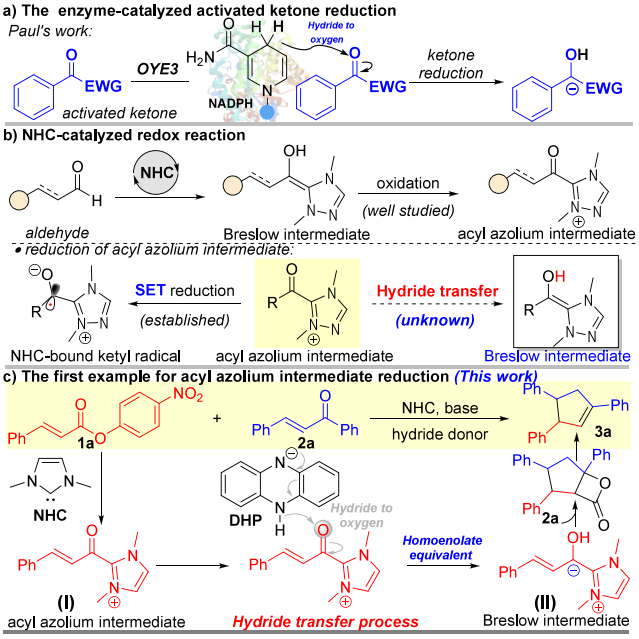


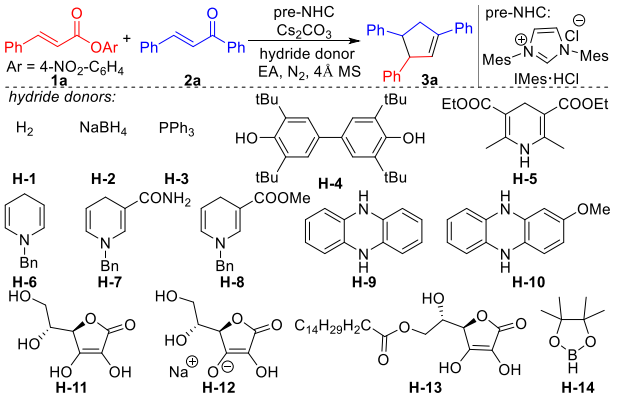
Figure 1. Common redox reactions and new acyl azolium reductive mode.

DHP served as a reductive precursor and must be deprotonated to generate the DHP anion, which acted as the actual reductant. Then, the DHP anion reduced acyl azolium intermediate **I** to Breslow intermediate **II** through hydride transfer. Subsequently, the Beslow intermediate reacted with chalcone, leading to the formation of cyclopentene. The desired cyclopentene product serves as a landmark, indicating the successful execution of the classic umpolung reaction (Figure 1c). To the best of our knowledge, our study constitutes the first success in transforming (unsaturated) carboxylic esters to the corresponding (unsaturated) Breslow intermediates, a challenge that remains formidable in the area of NHC catalysis. This new protocol can promote the carboxylic acid, and its derivates readily convert to various value-added fine chemicals.

Our study starts with activated carboxylic ester **1a** and chalcone **2a** as the model substrates to search for the suitable hydride donors (Scheme 1). Inspired by the biocatalyzed reduction approaches, various common reductants were explored, such as hydrogen (**H-1**), sodium borohydride (**H-2**), triphenylphosphine (**H-3**), and the reduced state of oxidant DQ (**H-4**). Meanwhile, other hydride donors, dihydropyridine analogues (**H-5**, **H-6**, **H-7**, and **H-8**), DHP analogues (**H-9** and **H-10**), Vitamin C analogues (**H-11**, **H-12**, and **H-13**), and pinacolborane (**H-14**), were also evaluated in reaction. However, only a trace amount of desired product **3a** could be observed by using **H-2**, **H-4**, and **H-8** as hydride donors (Scheme 1, entries 2, 4, and 8). To our surprise, the reaction efficiency was notably improved when **H-9** and **H-10** were used as hydride donors; practically, the desire product **3a** was obtained with 24% yield and 9:1 diastereomeric ratio (d.r.) via hydride donor **H-9**. This was an encouraging result and indicated a preliminary validation of our hypothesis.

We next performed the reactions with **H-9** as hydride donor to further search for optimal conditions under various NHC catalysts; the key results are summarized in Scheme 2. First, different NHC catalysts **A**, **B**, and **C** were investigated. The

Scheme 1. Initial Studies of Hydride Donors[a]



entry	hydride donor	yield(%)[b]	d.r.[c]
1	**H-1**	nr	-
2	**H-2**	<5%	-
3	**H-3**	nr	-
4	**H-4**	<5%	-
5	**H-5**	nr	-
6	**H-6**	nr	-
7	**H-7**	nr	-
8	**H-8**	<5%	-
9	**H-9**	24	9:1
10	**H-10**	15	5:1
11	**H-11**	nr	-
12	**H-12**	nr	-
13	**H-13**	nr	-
14	**H-14**	nr	-

[a]Unless otherwise specified, the reactions were carried out using **1a** (0.12 mmol, 1.20 equiv), **2a** (0.10 mmol, 1.00 equiv), base (0.12 mmol, 1.20 equiv), pre-NHC (0.02 mmol, 0.20 equiv), hydride donor (1.00 mmol, 1.00 equiv), and solvent (2.0 mL) at 30 °C for 12 h under the condition of a N_2 atmosphere. 4Å MS = 100.0 mg. nr = no reaction. [b]Isolated yield of **3a**. [c]The diastereomeric ratio (d.r.) of **3a** was estimated by ^{1}H NMR analysis.

yields of desired product **3a** decreased rapidly when triazolium **B** and **C** were employed (Scheme 2, entries 2 to 3). These results showed that pre-NHC **A** could be the most suitable catalyst to optimize the reaction conditions. Several organic and inorganic bases were examined here; the lower yields of product **3a** were obtained when Cs_2CO_3 was replaced by DBU and K_3PO_4 (Scheme 2, entries 4 to 5). Meanwhile, a diverse set of solvents was explored, and it was found that the yield of **3a** did not improve under other solvents (Scheme 2, entries 6 to 7). Subsequently, based on the result in Scheme 2, entry 1, reaction temperature was increased to 60 °C while increasing the equivalents of substrate **1a** (0.20 mmol), Cs_2CO_3 (0.22 mmol), and **H-9** (0.20 mmol). Afterward, the amount of solvent was also reduced (EA, 1.0 mL) (Scheme 2, entries 8 to 10). The target product **3a** was provided in 68% isolated yield and 8:1 d.r. (Scheme 2, entry 10).

With optimal reaction conditions (Scheme 2, entry 10) in hand, we explored the reaction scope of both activated carboxylic ester **1** and chalcone **2**. Initially, examples of the different ester substrates were examined (Scheme 3). The structure of **3a** was confirmed through X-ray diffraction analysis. The yield of the corresponding product was barely affected when the ester substrate was substituted with an electron-donating group (**3b**). Meanwhile, the phenyl ring was

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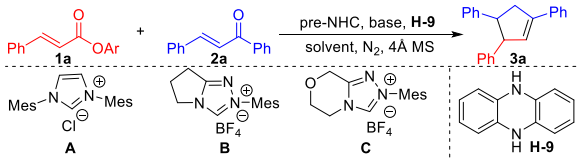
Scheme 2. Optimization of Reaction Conditions[a]



entry	NHC	base	solvent	yield(%)[b]	d.r.[c]
1	**A**	Cs_2CO_3	EA	24	9:1
2	**B**	Cs_2CO_3	EA	7	5:1
3	**C**	Cs_2CO_3	EA	8	8:1
4	**A**	DBU	EA	14	4:1
5	**A**	K_3PO_4	EA	5	13:1
6	**A**	Cs_2CO_3	Toluene	10	>20:1
7	**A**	Cs_2CO_3	THF	18	6:1
8[d]	**A**	Cs_2CO_3	EA	31	6:1
9[d,e]	**A**	Cs_2CO_3	EA	45	12:1
10[d,e,f]	**A**	Cs_2CO_3	EA	68	8:1

[a]Unless otherwise specified, the reactions were carried using **1a** (0.12 mmol, 1.20 equiv), **2a** (0.10 mmol, 1.00 equiv), base (0.12 mmol, 1.20 equiv), pre-NHC (0.02 mmol, 0.20 equiv), hydride donor (1.00 mmol, 1.00 equiv), and solvent (2.0 mL) at 30 °C for 12 h under the condition of a N_2 atm. 4Å MS = 100.0 mg. [b]Isolated yield of **3a**. [c]The diastereomeric ratio (d.r.) of **3a** was estimated by ^{1}H NMR analysis. [d]Reaction temperature: 60 °C. [e]**1a** (0.20 mmol, 2.00 equiv), Cs_2CO_3 (0.22 mmol, 2.20 equiv), and **H-9** (0.20 mmol, 2.00 equiv) were used. [f]EA = 1.0 mL.

substituted with electron-withdrawing groups such as chrolo- and bromo-atoms and a trifluoromethyl group, and the corresponding products were synthesized (**3c** to **3h**). Replacement with a naphthyl group afforded **3i** in 57% yield with a high d.r. value. Then, heterocyclic groups such as thiophene and furan were also evaluated in these reactions, obtaining acceptable yields and good d.r. values (**3j** to **3k**). The examples of the substituent chalcones were also examined, and the corresponding product **3l** was obtained with good yield and d.r. value when the R^2 group was a methyl substituent. The higher yields can be observed when the para-position of the phenyl ring was substituted with electron-withdrawing groups (up to 84% yield) (**3m** to **3p**). At the same time, various R^3 groups were also studied, and the corresponding products with electron-donating groups (**3q** to **3t**) were successfully obtained. Furthermore, it showed high reactivity for substrates with electron-withdrawing groups (**3u** to **3x**). It is worth noting that the heteroaromatic groups were also tolerated in chalcone with the reaction conditions and the yields of desired products were acceptable (**3y** to **3z**, **3aa** to **3ab**). Meanwhile, multisubstituted chalcone substrates were also investigated, and higher to excellent yields were obtained (**3ac** to **3ae**).

Furthermore, using the triazolium pre-NHC **H** (0.02 mmol) gave product **3ae*** in 61% yield (7:1 d.r.) and 70:30 e.r., which implies the possibility but challenge for the enantioselective reactions (Scheme 4). Then, the model reaction was successfully scaled up 10 times using **1a** (0.54 g, 2.00 mmol) and **2a** (0.21 g, 1.00 mmol); under the model reaction conditions, **3a** can be obtained in 48% yield and 5:1 d.r. In addition, we have successfully realized the reduction of the double bond in **3a** to give cyclopentane **4** in quantitative yield (Scheme 5).

To understand the mechanism, liquid chromatography-high resolution mass spectroscopy (LC-HRMS) was employed to detect key intermediates in the model reaction (Figure 2a). The acyl azolium intermediate presents three possible hydride acceptor sites, leading to the formation of three isomers (intermediates **II**, **III**, and **III′**). Under the modified model reaction condition (w/o chalcone), the total ion chromatogram (TIC) of crude reaction was recorded, and the extracted ion chromatogram (XIC) was obtained by extracting m/z = 437.2587 (±5 ppm), which corresponds to the exact mass-to-charge ratio of the Breslow intermediate II. According to above result, two peaks, A (R_t = 7.01 min) and B (R_t = 8.47 min) were observed in the extracted ion chromatogram at m/z = 437.2587 (±5 ppm). However, the intermediates **II**, **III**, and **III′** were isomers; it was difficult to directly distinguish these intermediates based solely on the mass-to-charge ratio. Fortunately, in our previous work, it was demonstrated that the Breslow intermediate could be synthesized using DBU as a strong base to avoid β-protonated byproducts (Supporting Information).[55−57] This method allowed for the unambiguous detection of the Breslow intermediate via LC-HRMS.[58] Peak A can be identified as Breslow intermediate **II** (R_t = 7.01 min), and additional experimental and computational mechanistic studies were performed to identify the remaining possible isomers.

Furthermore, three possible reaction pathways were evaluated through theoretical calculations,[59−61] as shown in Figure 2b. Hydride transfer to the oxygen atom of carbonyl in acyl azolium intermediate **I** to afford Breslow intermediate **II** was found to be the most favorable, with a Gibbs free energy barrier of **TS1** ($\Delta G^{\ddagger}$ = 5.1 kcal/mol). In addition, the carbonyl carbon inacyl azolium intermediate **I** could not serve as the hydride acceptor, with the corresponding Gibbs energy barrier ($\Delta G^{\ddagger}$ = 26.6 kcal/mol) being unfavorable. Meanwhile, the C═C double bond in acyl azolium intermediate **I** could be reduced, and the energy barrier of **TS4** ($\Delta G^{\ddagger}$ = 13.8 kcal/mol) was slightly higher than that of **TS1**. To further confirm the possibility of hydride transfer to the C═C double bond, deuterium-labeled substrate **1a** (**D**) was synthesized and employed to react with chalcone **2a** under model reaction conditions. The desired product **3a** (**D**) was obtained in 60% yield (10:1 d.r.), with 80% deuterium rate remaining at the corresponding position (Figure 2c). The results indicated that the C═C double bond in the acyl azolium intermediate **I** could not be reduced by hydride donor **H-9**. Therefore, peak B in Figure 2a may be identified as intermediate **III′**, which was generated via protonation of Breslow intermediate **II**. Meanwhile, the D-labeled hydride donor **H-9** (**D**) (40% D) was synthesized. Then, **H-9** (**D**) was used in model reaction access to product **3a** (58% yield and 7:1 d.r.); it indicated that the deuterium could not be found in product **3a** (Figure 2c). According to this result, the hydride transfers to the oxygen atom of the carbonyl in the acyl azolium intermediate, which is consistent with our proposed reaction mechanism.

Based on the above experimental and computational results, the proposed mechanism is shown in Figure 2d. In this reaction, the NHC catalyst reacted with α,β-unsaturated carboxylic ester **1a** to generate the corresponding acyl azolium intermediate **I**. Meanwhile, 5,10-dihydro-phenazine (**H-9**), DHP, can be deprotonated to form the DHP anion, which was employed as the hydride source. Furthermore, the acyl azolium intermediate **I** was reduced by a DHP anion to afford the Breslow intermediate **II** via hydride transfer. Subsequently, a

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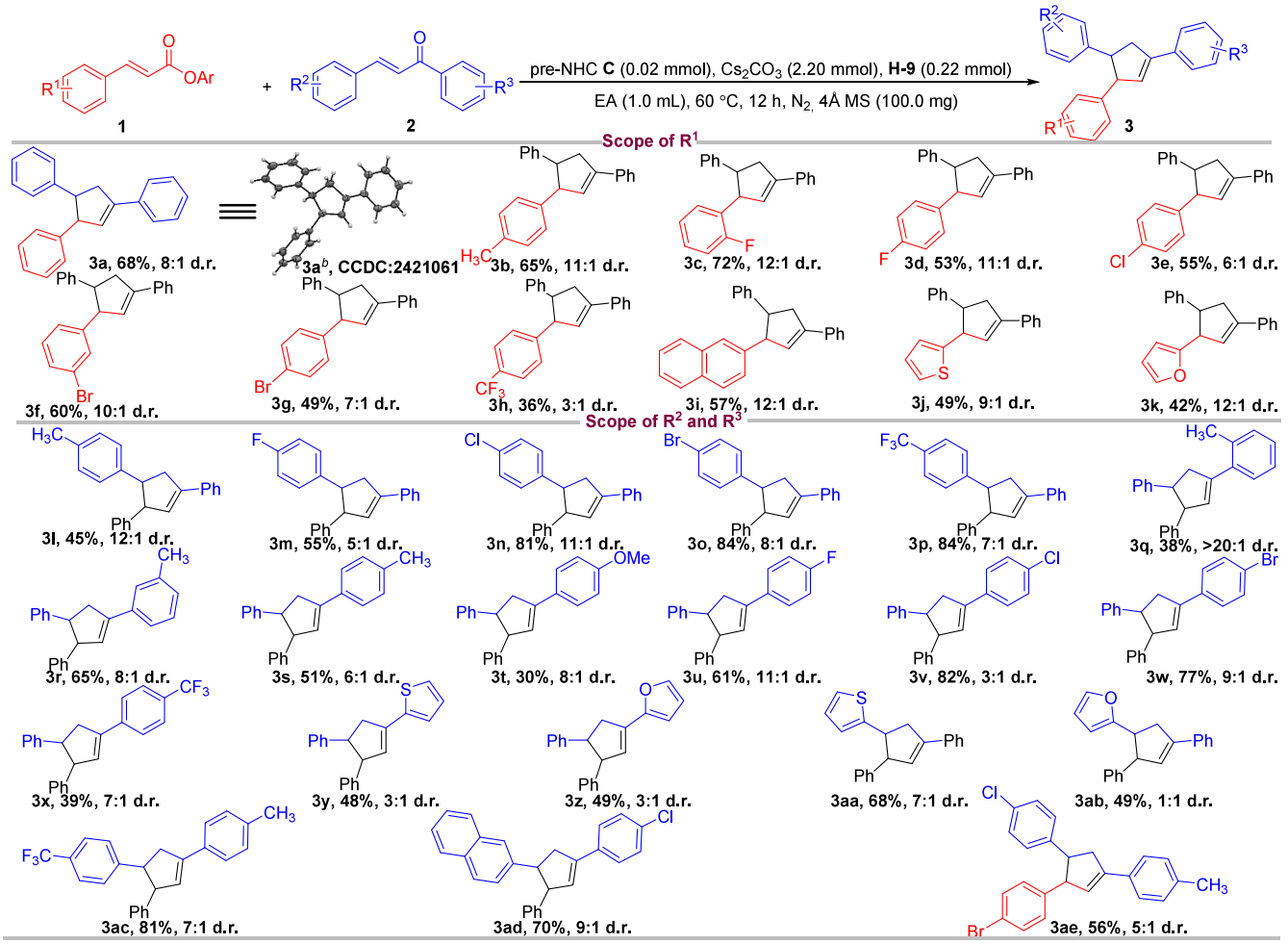
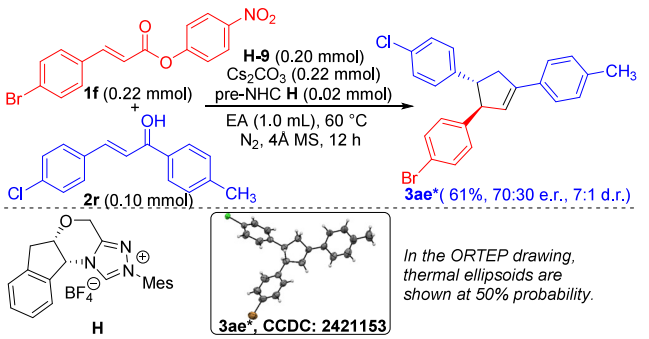
Scheme 3. Examples of Ester and Chalcone Substrates[a]

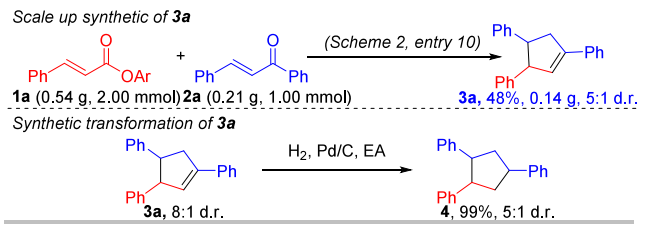


[a]Reaction conditions as stated in Scheme 2, entry 10. Yields are isolated yields after purification by column chromatography, and d.r. values are determined via ^{1}H NMR analysis. [b]In the ORTEP drawing, thermal ellipsoids are shown at 50% probability (CCDC 2421061).

Scheme 4. Primitive Enantioselective Reaction



Scheme 5. Synthetic Application



classical umpolung reaction was performed between Breslow intermediate **II** and chalcone **2a**, resulting in the formation of cyclopentene **3a**, which was a key marker for the formation of Breslow intermediate **II**.

Conclusions

In summary, we have established a novel carbene-catalyzed reductive model. The reductive NHC catalysis via hydride transfer enables the generation of homoenolates from unsaturated esters, in which acyl azolium intermediates can serve as a weak oxidant to accept the hydride, thereby generating the desired Breslow intermediates. In the reaction, activated carboxylic esters reacted with the NHC catalyst to form an acyl azolium intermediate. The $FMNH_2$-type reductant DHP was employed as the hydride source to reduce the acyl azolium intermediate, and the key process was believed to involve a hydride transfer from DHP to the oxygen atom of the acyl azolium carbonyl and generate the corresponding desired Breslow intermediate. Both experimental and computational studies were conducted, confirming the key intermediates through LC-HRMS analysis and providing the Gibbs free energy profiles for the key steps in the novel carbene-catalyzed reduction. Inspired by these significant findings, ongoing studies in our group focus on the in situ carbene-catalyzed reduction of carboxylic acids and their

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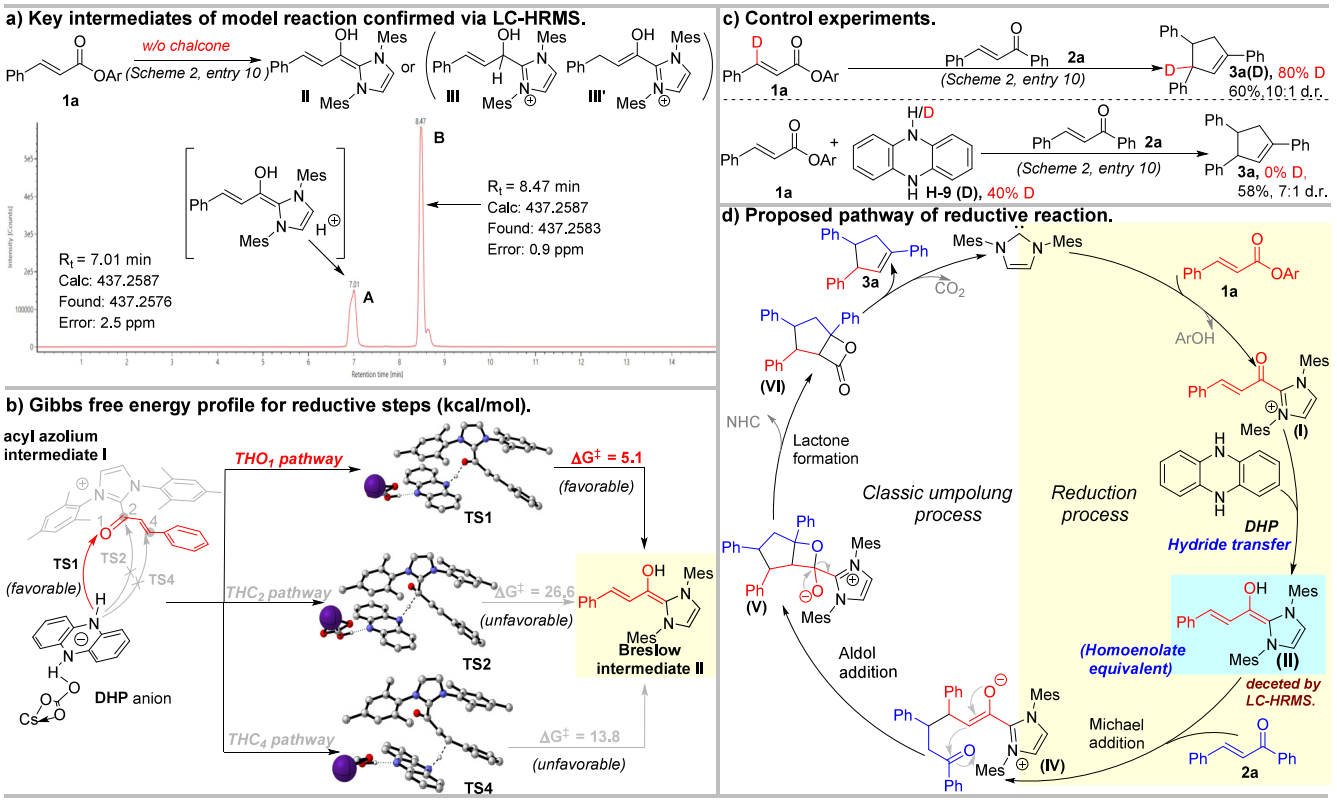

Figure 2. Additional supporting mechanistic experiments and proposed catalytic cycle.

derivatives to aldehydes, with the goal of applying this new reductive protocol to the synthesis of pharmaceuticals and agrochemicals.

Methods

General Procedure for the Enantioselective Synthesis of 3. To a dry 4.0 mL vial equipped with a magnetic stir bar, carboxylic ester **1** (0.20 mmol, 2.00 equiv), chalcone **2** (0.10 mmol, 1.00 equiv), pre-NHC **A** (0.02 mmol, 0.20 equiv), and Cs_2CO_3 (0.22 mmol, 2.20 equiv) were added. The vial was then sealed, purged, and backfilled with N_2 three times in a glovebox before adding **H-9** (0.20 mmol, 2.00 equiv), 4 Å MS (100.0 mg), and dry ethyl ester (1.0 mL). The reaction mixture was then stirred at 60 °C in an oil bath for 12 h (monitored by TLC). The mixture was concentrated under reduced pressure. The crude residue was purified via column chromatography on silica gel (petroleum ether) to afford the desired product **3**.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c01604.

Detailed experimental procedures and spectroscopic data (NMR, MS, and HPLC) for compounds, computational details, and X-ray crystallographic data (PDF)

Accession Codes

Deposition Numbers 2421061 and 2421153 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Toogood, H. S.; Gardiner, J. M.; Scrutton, N. S. Biocatalytic reductions and chemical versatility of the old yellow enzyme family of flavoprotein oxidoreductases. *ChemCatChem.* **2010**, *2*, 892−914.
(2) Hollmann, F.; Arends, I. W. C. E.; Holtmann, D. Enzymatic reductions for the chemist. *Green Chem.* **2011**, *13*, 2285−2314.
(3) Delfau, L.; Nichilo, S.; Molton, F.; Broggi, J.; Tomas-Mendivil, E.; Martin, D. Critical assessment of the reducing ability of Breslow type derivatives and implications for carbene-catalyzed radical reactions. *Angew. Chem., Int. Ed.* **2021**, *60*, 26783−26789.
(4) Hollmann, F.; Opperman, D. J.; Paul, C. E. Biocatalytic reduction reactions from a chemist's perspective. *Angew. Chem., Int. Ed.* **2021**, *60*, 5644−5665.
(5) Rowshanpour, R.; Gravel, M.; Dudding, T. N-heterocyclic carbene organocatalyzed redox-active/ring expansion reactions: mechanistic insights unveiling base cooperativity. *J. Org. Chem.* **2022**, *87*, 16785−16793.
(6) Padhi, S. K.; Bougioukou, D. J.; Stewart, J. D. Site-saturation mutagenesis of tryptophan 116 of saccharomyces pastorianus old yellow enzyme uncovers stereocomplementary variants. *J. Am. Chem. Soc.* **2009**, *131*, 3271−3280.
(7) Daugherty, A. B.; Govindarajan, S.; Lutz, S. Improved biocatalysts from a synthetic circular permutation library of the flavin dependent oxidoreductase old yellow enzyme. *J. Am. Chem. Soc.* **2013**, *135*, 14425−14432.
(8) Lonsdale, R.; Reetz, M. T. Reduction of α,β-unsaturated ketones by old yellow enzymes: mechanistic insights from quantum mechanics/ molecular mechanics calculations. *J. Am. Chem. Soc.* **2015**, *137*, 14733−14742.
(9) Amato, E. D.; Stewart, J. D. Applications of protein engineering to members of the old yellow enzyme family. *Biotechnol. Adv.* **2015**, *33*, 624−631.
(10) Robescu, M. S.; Cendron, L.; Bacchin, A.; Wagner, K.; Reiter, T.; Janicki, I.; Merusic, K.; Illek, M.; Aleotti, M.; Bergantino, E.; Hall, M. Asymmetric proton transfer catalysis by stereocomplementary old yellow enzymes for C = C Bond isomerization reaction. *ACS Catal.* **2022**, *12*, 7396−7405.
(11) Stuermer, R.; Hauer, B.; Hall, M.; Faber, K. Asymmetric bioreduction of activated C = C bonds using enoate reductases from the old yellow enzyme family. *Curr. Opin. Chem. Biol.* **2007**, *11*, 203−213.
(12) Scholtissek, A.; Tischler, D.; Westphal, A.; Van Berkel, W.; Paul, C. Old yellow enzyme-catalysed asymmetric hydrogenation: linking family roots with improved catalysis. *Catalysts* **2017**, *7*, 130.
(13) Toogood, H. S.; Scrutton, N. S. Discovery, Characterization, engineering, and applications of ene-reductases for industrial biocatalysis. *ACS Catal.* **2018**, *8*, 3532−3549.
(14) Vaz, A. D. N.; Chakraborty, S.; Massey, V. Old yellow enzyme: aromatization of cyclic enones and the mechanism of a novel dismutation reaction. *Biochemistry* **1995**, *34*, 4246−4256.
(15) Lee, S. H.; Choi, D. S.; Pesic, M.; Lee, Y. W.; Paul, C. E.; Hollmann, F.; Park, C. B. Cofactor-free, direct photoactivation of enoate reductases for the asymmetric reduction of C = C bonds. *Angew. Chem., Int. Ed.* **2017**, *56*, 8681−8685.
(16) Litman, Z. C.; Wang, Y.; Zhao, H.; Hartwig, J. F. Cooperative asymmetric reactions combining photocatalysis and enzymatic catalysis. *Nature* **2018**, *560*, 355−359.
(17) Heckenbichler, K.; Schweiger, A.; Brandner, L. A.; Binter, A.; Toplak, M.; Macheroux, P.; Gruber, K.; Breinbauer, R. Asymmetric reductive carbocyclization using engineered ene reductases. *Angew. Chem., Int. Ed.* **2018**, *57*, 7240−7244.
(18) Biegasiewicz, K. F.; Cooper, S. J.; Gao, X.; Oblinsky, D. G.; Kim, J. H.; Garfinkle, S. E.; Joyce, L. A.; Sandoval, B. A.; Scholes, G. D.; Hyster, T. K. Photoexcitation of flavoenzymes enables a stereoselective radical cyclization. *Science* **2019**, *364*, 1166−1169.
(19) Bender, S. G.; Hyster, T. K. Pyridylmethyl radicals for enantioselective alkene hydroalkylation using "ene"-reductases. *ACS Catal.* **2023**, *13*, 14680−14684.
(20) Wang, X.; Saba, T.; Yiu, H. H. P.; Howe, R. F.; Anderson, J. A.; Shi, J. Cofactor NAD(P)H Regeneration Inspired by heterogeneous pathways. *Chem.* **2017**, *2*, 621−654.
(21) Selles Vidal, L.; Kelly, C. L.; Mordaka, P. M.; Heap, J. T. Review of NAD(P)H-dependent oxidoreductases: properties, engineering and application. *BBA-Proteins and Proteomics* **2018**, *1866*, 327−347.
(22) Yuan, B.; Yang, D.; Qu, G.; Turner, N. J.; Sun, Z. Biocatalytic reductive aminations with NAD(P)H-dependent enzymes: enzyme discovery, engineering and synthetic applications. *Chem. Soc. Rev.* **2024**, *53*, 227−262.
(23) Sahrawat, A. S.; Polidori, N.; Kroutil, W.; Gruber, K. Deciphering the unconventional reduction of C = N bonds by old yellow enzymes using QM/MM. *ACS Catal.* **2024**, *14*, 1257−1266.
(24) Velikogne, S.; Breukelaar, W. B.; Hamm, F.; Glabonjat, R. A.; Kroutil, W. C = C-ene-reductases reduce the C = N bond of oximes. *ACS Catal.* **2020**, *10*, 13377−13382.
(25) Breukelaar, W. B.; Polidori, N.; Singh, A.; Daniel, B.; Glueck, S. M.; Gruber, K.; Kroutil, W. Mechanistic insights into the ene reductase-catalyzed promiscuous reduction of oximes to amines. *ACS Catal.* **2023**, *13*, 2610−2618.
(26) Wolder, A. E.; Heckmann, C. M.; Hagedoorn, P.-L.; Opperman, D. J.; Paul, C. E. Asymmetric monoreduction of α,β-dicarbonyls to α-hydroxy carbonyls by ene reductases. *ACS Catal.* **2024**, *14*, 15713−15720.
(27) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485−496.
(28) Menon, R. S.; Biju, A. T.; Nair, V. Recent advances in employing homoenolates generated by N-heterocyclic carbene (NHC) catalysis in carbon-carbon bond-forming reactions. *Chem. Soc. Rev.* **2015**, *44*, 5040−5052.
(29) Zhang, C.; Hooper, J. F.; Lupton, D. W. N-Heterocyclic carbene catalysis via the α,β-unsaturated acyl azolium. *ACS Catal.* **2017**, *7*, 2583−2596.
(30) Mondal, S.; Yetra, S. R.; Mukherjee, S.; Biju, A. T. NHC catalyzed generation of α,β-unsaturated acylazoliums for the enantioselective synthesis of heterocycles and carbocycles. *Acc. Chem. Res.* **2019**, *52*, 425−436.
(31) Chakraborty, S.; Barik, S.; Biju, A. T. N-Heterocyclic carbene (NHC) organocatalysis: from fundamentals to frontiers. *Chem. Soc. Rev.* **2025**, *54*, 1102−1124.

https://doi.org/10.1021/acs.orglett.5c01604
Org. Lett. XXXX, XXX, XXX−XXX

(32) Zhao, X.; Ruhl, K. E.; Rovis, T. N-Heterocyclic-carbene catalyzed asymmetric oxidative hetero-diels-alder reactions with simple aliphatic aldehydes. *Angew. Chem., Int. Ed.* **2012**, *51*, 12330−12333.
(33) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. Enantioselective synthesis of spirocyclohexadienones by NHC catalyzed formal [3 + 3] annulation reaction of enals. *Angew. Chem., Int. Ed.* **2016**, *55*, 268−272.
(34) Wu, X.; Zhang, Y.; Wang, Y.; Ke, J.; Jeret, M.; Reddi, R. N.; Yang, S.; Song, B. A.; Chi, Y. R. Polyhalides as efficient and mild oxidants for oxidative carbene organocatalysis by radical processes. *Angew. Chem., Int. Ed.* **2017**, *56*, 2942−2946.
(35) Deng, R.; Wu, S.; Mou, C.; Liu, J.; Zheng, P.; Zhang, X.; Chi, Y. R. Carbene-catalyzed enantioselective sulfonylation of enone aryl aldehydes: a new mode of Breslow intermediate oxidation. *J. Am. Chem. Soc.* **2022**, *144*, 5441−5449.
(36) Zhou, P.; Li, W.; Lan, J.; Zhu, T. Electroredox carbene organocatalysis with iodide as promoter. *Nat. Commun.* **2022**, *13*, 3827.
(37) Zhang, Y.; Du, Y.; Huang, Z.; Xu, J.; Wu, X.; Wang, Y.; Wang, M.; Yang, S.; Webster, R. D.; Chi, Y. R. N-Heterocyclic carbene catalyzed radical reactions for highly enantioselective β hydroxylation of enals. *J. Am. Chem. Soc.* **2015**, *137*, 2416−2419.
(38) Wang, Y.; Du, Y.; Huang, X.; Wu, X.; Zhang, Y.; Yang, S.; Chi, Y. R. Carbene-catalyzed reductive coupling of nitrobenzyl bromide and nitroalkene via the single-electron-transfer (SET) process and formal 1,4-addition. *Org. Lett.* **2017**, *19*, 632−635.
(39) Li, Q. Z.; Zeng, R.; Han, B.; Li, J. L. Single-electron transfer reactions enabled by N-heterocyclic carbene organocatalysis. *Chem.—Eur. J.* **2021**, *27*, 3238−3250.
(40) Liu, K.; Schwenzer, M.; Studer, A. Radical NHC catalysis. *ACS Catal.* **2022**, *12*, 11984−11999.
(41) Meng, Q. Y.; Döben, N.; Studer, A. Cooperative NHC and photoredox catalysis for the synthesis of β-trifluoromethylated alkyl aryl ketones. *Angew. Chem., Int. Ed.* **2020**, *59*, 19956−19960.
(42) Prentice, C.; Morrison, J.; Zysman-Colman, E.; Smith, A. D. Dual NHC/photoredox catalytic synthesis of 1,4-diketones using an MR TADF photocatalyst (DiKTa). *Chem. Commun.* **2022**, *58*, 13624−13627.
(43) Bay, A. V.; Scheidt, K. A. Single-electron carbene catalysis in redox processes. *Trends Chem.* **2022**, *4*, 277−290.
(44) Rourke, M. J.; Wang, C. T.; Schull, C. R.; Scheidt, K. A. Acyl azolium-photoredox-enabled synthesis of β-keto sulfides. *ACS Catal.* **2023**, *13*, 7987−7994.
(45) Zhu, J. L.; Schull, C. R.; Tam, A. T.; Rentería-Gómez, Á.; Gogoi, A. R.; Gutierrez, O.; Scheidt, K. A. Photoinduced acylations via azolium-promoted intermolecular hydrogen atom transfer. *J. Am. Chem. Soc.* **2023**, *145*, 1535−1541.
(46) Byun, S.; Hwang, M. U.; Wise, H. R.; Bay, A. V.; Cheong, P. H. Y.; Scheidt, K. A. Light-driven enantioselective carbene-catalyzed radical-radical coupling. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202312829.
(47) Toogood, H. S.; Scrutton, N. S. New developments in 'ene' reductase catalysed biological hydrogenations. *Curr. Opin. Chem. Biol.* **2014**, *19*, 107−115.
(48) Winkler, C. K.; Faber, K.; Hall, M. Biocatalytic reduction of activated C C-bonds and beyond: emerging trends. *Curr. Opin. Chem. Biol.* **2018**, *43*, 97−105.
(49) Aleku, G. A. Imine reductases and reductive aminases in organic synthesis. *ACS Catal.* **2024**, *14*, 14308−14329.
(50) De Risi, C.; Brandolese, A.; Di Carmine, G.; Ragno, D.; Massi, A.; Bortolini, O. Oxidative N-Heterocyclic carbene catalysis. *Chem.—Eur. J.* **2023**, *29*, No. e202202467.
(51) Mondal, S.; Ghosh, A.; Biju, A. T. N-heterocyclic carbene (NHC) catalyzed transformations involving azolium enolates. *Chem. Rec.* **2022**, *22*, No. e202200054.
(52) Werther, T.; Wahlefeld, S.; Salewski, J.; Kuhlmann, U.; Zebger, I.; Hildebrandt, P.; Dobbek, H. Redox-dependent substrate-cofactor interactions in the michaelis-complex of a flavin-dependent oxidoreductase. *Nat. Commun.* **2017**, *8*, 16084.
(53) Heckenbichler, K.; Schweiger, A.; Brandner, L. A.; Binter, A.; Toplak, M.; Macheroux, P.; Gruber, K.; Breinbauer, R. Asymmetric reductive carbocyclization using engineered ene reductases. *Angew. Chem., Int. Ed.* **2018**, *57*, 7240−7244.
(54) Saeed, T. S.; Albalawi, S. S.; Abuhagr, A.; Althobaiti, S. A.; Hassanain, H. M.; Reeves, D. M.; Abdullah, M. R.; Sinn, E. Two electron transfer photoreduction of methyl viologen and perfluorooctanoic acid mediated by flavin mononucleotide at colloidal titanium dioxide interfaces. *New J. Chem.* **2023**, *47*, 21661−21669.
(55) Burstein, C.; Glorius, F. Organocatalyzed conjugate umpolung of alpha, beta-unsaturated aldehydes for the synthesis of gamma butyrolactones. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205−6208.
(56) He, M.; Bode, J. W. Catalytic synthesis of gamma-lactams via direct annulations of enals and N-sulfonylimines. *Org. Lett.* **2005**, *7*, 3131−3134.
(57) Sohn, S. S.; Bode, J. W. Catalytic generation of activated carboxylates from enals: a product-determining role for the base. *Org. Lett.* **2005**, *7*, 3873−3876.
(58) Wang, Q.; Wu, S.; Zou, J.; Liang, X.; Mou, C.; Zheng, P.; Chi, Y. R. NHC-catalyzed enantioselective access to β-cyano carboxylic esters via in situ substrate alternation and release. *Nat. Commun.* **2023**, *14*, 4878.
(59) Wang, X.; Li, S. J.; Wang, Y. N.; Wei, D.; Lan, Y. Theoretical model for N-Heterocyclic carbene-catalyzed desymmetrizing [4 + 1] and [4 + 2] annulations of an enal and aryldialdehyde with 1,3-cyclopentenedione. *Org. Lett.* **2021**, *23*, 2421−2425.
(60) Shi, Q.; Pei, Z.; Song, J.; Li, S.-J.; Wei, D.; Coote, M. L.; Lan, Y. Diradical generation via relayed proton-coupled electron transfer. *J. Am. Chem. Soc.* **2022**, *144*, 3137−3145.
(61) Deng, Y.; Wang, X.; Liu, H.; Cai, H.; Song, C.; Chi, Y. R.; Wei, D.; Jin, Z. N-Heterocyclic carbene-catalyzed chemo- and enantioselective three-component esterification/amidation relay for access to planar chiral ferrocene derivatives. *ACS Catal.* **2025**, *15*, 6130−6140.

https://doi.org/10.1021/acs.orglett.5c01604
Org. Lett. XXXX, XXX, XXX−XXX