Switchable organocatalysis from *N*-heterocyclic carbene-carbodiimide adducts with tunable release temperature

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ABSTRACT: *N*-Heterocyclic carbenes (NHCs) are powerful organocatalysts, but their air sensitivity often requires in situ generation from a stable precursor. Previous "masked" NHC systems suffer from incomplete latency, irreversible release, and/or changing the NHC structure to control both catalyst release and catalyst activity. Herein, we utilize tunable carbodiimides (CDIs) as NHC masks to orthogonally control release from activity. Using a common imidazolylidene NHC, we show that CDI masks can achieve switchable organocatalysis and that small electronic perturbations only to the CDI result in a >10 °C shift in activation temperature. This platform will enable more precise control over NHC activation than previous systems.

Regulating catalytic activity is a grand challenge in homogeneous catalysis as synthetic chemists attempt to mimic enzymatic control over chemical reactions.[1,2] This challenge has led to the field of switchable catalysis,[2–4] which promotes advanced (spatio)temporal control over a variety of organic[5–8] and polymerization[9–12] reactions. Reversible coordination is one common strategy to protect (i.e., "mask" the reactivity of) a catalyst in a stable, inactive state before an external stimulus – such as heat, light, or the addition of a chemical compound – converts the catalyst into its active form (Figure 1). A variety of metal,[6,13,14] supramolecular,[15,16] and organocatalysts[17–19] have used this approach, oftentimes achieving both high activity and increased catalyst lifetime.

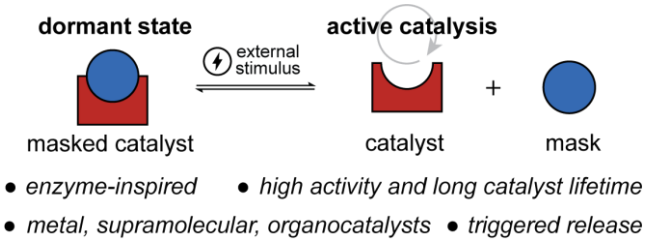


Figure 1. Regulating catalytic activity via reversible binding (i.e. "masked catalysis").

N-Heterocyclic carbenes (NHCs) are highly versatile organocatalysts[20–25] that are particularly amenable to this reversible-coordination strategy because the mask can mitigate challenges caused by NHCs' instability to air.[26–28] Masked NHC adducts avoid the traditional method of using stoichiometric/excess base to deprotonate an NHC salt precursor in situ, which often requires demanding purification and can lead to undesired side reactions.[27,29] A variety of masks have been explored for NHC organocatalysis. Lewis acidic metals[30–33] provide facile tuning and occasionally cooperative catalysis, but their inclusion precludes true "metal-free" organocatalysis, and some systems suffer from incomplete latency or chemical incompatibilities. Metal-free masks include hydrogen carbonate salts,[34–36] alcohols,[37] water,[38] and halogenated organic compounds;[39,40] however, many of these systems fail to produce full latency with moderate release temperatures.

The most popular and well-studied masked NHCs are carboxylate adducts due to their latency, wide applicability, and facile synthesis (Figure 2A).[27,41–43] While NHC-CO_2 adduct formation is reversible in a closed system,[44,45] CO_2 gas normally evolves out of solution upon heating. This phenomenon drives the release of the NHC but also prevents reversible catalyst re-capture in situ. Furthermore, CO_2 is a

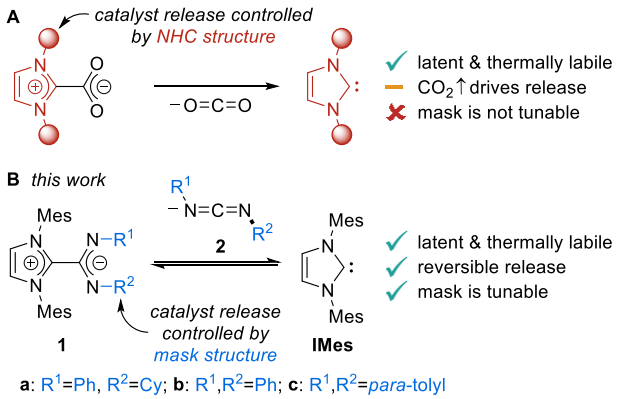


Figure 2. (A) Common NHC-carboxylate adducts used for latent catalysis. (B) NHC-CDI adducts as masked organocatalysts.

simple, non-tunable molecule which necessitates that the highly modular structure[46,47] of the NHC is used to tune latency[41] and solubility[48] in addition to its reactivity.[49] Coupling these variables often leads to an undesirable trade-off between latency and catalyst activity.[50,51] Isothiocyanates have similarly been used to mask NHCs, with the modular nitrogen substituent shown to slightly affect the adduct stability without changing the NHC structure.[52] While the NHC-isothiocyanate adducts were stable at room temperature, the adduct formation was too strong, such that temperatures above 100 °C were required to achieve >5% conversion in 2 hours.

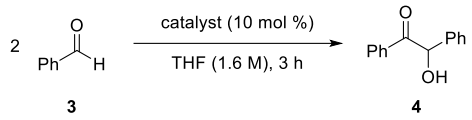
Herein, we establish a new platform for regulating NHC organocatalytic activity using carbodiimide (CDI) masks, which are isoelectronic to CO_2 and isothiocyanates but are highly tunable due to the two nitrogen substituents (Figure 2B). NHC-CDI betaine adducts[53] have attracted attention as amidinate-type ligands for discrete metal complexes[54–57] or functionalized nanoparticle surfaces,[58–60] in polyzwitterionic materials,[40] as mechanophores,[61] and for C–Cl bond activation,[57,62] but have yet to be applied to masked organocatalysis. We envision that the wider range of adduct stabilities accessible using this platform will enable orthogonal and more precise control over NHC activation for organocatalysis compared to previous systems.

For our model system, 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (**IMes**) was chosen as the test NHC due to its common use in organocatalysis.[20,25] We hypothesized that a highly dynamic adduct would be required to intercept the free NHC for catalysis. Previously, Johnson and coworkers[40,63] have shown that *N*-alkyl-*N*′-aryl CDIs result in more dynamic adducts than *N*,*N*′-diaryl CDIs. Therefore, we initially chose *N*-cyclohexyl-*N*′-phenyl CDI (**2a**) as the mask for **IMes** and synthesized the corresponding adduct **1a**. We confirmed the structure of **1a** via X-ray crystallography and verified the dynamics by measuring the dissociation constant (k_d) for CDI exchange with *N*,*N*′-di(*p*-tolyl) CDI (**2c**) (Figures S1–S2).[64] For comparison, the **IMes** adduct with *N*,*N*′-diphenyl CDI (**1b**) was less dynamic due to the two aryl substituents, as expected (Figures S3–S4).[40]

Having a dynamic adduct in hand, we then sought to explore NHC-CDIs as competent pre-catalysts in the classic benzoin condensation,[65,66] which displays the characteristic umpolung reactivity of NHC organocatalysis[47,67,68] through the formation of an acyl anion equivalent (i.e., Breslow intermediate).[69] In our proof-of-concept experiment, we observed that adding **1a** to benzaldehyde in THF resulted in 92% conversion of starting material to the desired product[64] in 3 h at 22 °C (Table 1, entry 1). No reaction was detected when **1a** was used at a lower reaction temperature (−34 °C, entry 2) whereas free **IMes** readily catalyzes this reaction at both 22 and −34 °C, with 91 and 65% conversion, respectively (entries 3–4). These data validate the hypothesis that a CDI can indeed mask NHC reactivity at low temperatures without interfering with the catalysis at a higher temperature.

While the *N*-alkyl-*N*′-aryl CDI mask of **1a** achieved temperature control over reactivity, this pre-catalyst is not ideal because the room temperature activity prevents ambient storage and handling. Therefore, we shifted our focus to the less dynamic *N*,*N*′-diphenyl CDI adduct (**1b**) in the hopes of discovering a catalytic system that is latent at room temperature. Gratifyingly, using **1b** as the pre-catalyst resulted in the desired latency at 22 °C (Table 1, entry 5) and high activity (83% conversion in 3 h) at 80 °C (entry 6, see Table S1 for more temperature trials). Control experiments adding no pre-catalyst or just the CDI **2b** resulted in no reaction at 80 °C (entry 7–8), indicating that an NHC catalyst is necessary to carry out the benzoin condensation, as expected. Unfortunately, the 80 °C activation temperature of **1b** was also not ideal because the benzoin condensation is known to have side reactions above 65 °C.[70]

Table 1. Using NHC-CDIs as pre-catalysts for the benzoin condensation[a]



3 **4**

entry	catalyst	temp. (°C)	% conv. of **3** to **4**[b]
1	**1a**	22	92
2	**1a**	−34	<1
3	**IMes**[c]	22	91
4	**IMes**[c]	−34	65
5	**1b**	22	<1
6	**1b**	80	83
7	none	80	<1
8	**2b**	80	<1
9	**1c**	65	86
10	**1c**	22	<1

[a]Conditions: benzaldehyde (26.5 mg, 0.250 mmol), catalyst (10 mol %), in THF (1.6 M), 3 h. [b]Determined by the ^{1}H NMR spectrum of the crude reaction mixture. [c]**IMes** added as the isolated carbene by deprotonation of **IMes**–H^+Cl^- using potassium bis(trimethylsilyl)amide (KHMDS).[64]

To avoid these side reactions, we sought to lower the catalyst activation temperature by adding more electron-donating substituents on the mask. We hypothesized that these substituents would weaken the adduct bond by decreasing the electrophilicity of the central CDI carbon, analogous to what was observed with the isothiocyanate-masked NHCs.[52] We synthesized adduct **1c,** which contains the more electron rich CDI **2c**. Excitingly, **1c** resulted in 86% conversion in 3 h at 65 °C (entry 9) while maintaining latency at room temperature (entry 10, see Table S1 for more temperature trials). These data confirm that activation temperature can be tuned entirely based on perturbations to the mask structure, orthogonally from changing the NHC catalyst as has been done in the past.[41,44]

Because NHC-CDI adducts are known to be nucleophilic through the amidinate nitrogens,[57,62] we wanted to test the possibility that the entire NHC-CDI was the active catalyst. We changed the NHC portion of **1c** to the more nucleophilic, saturated analog **SIMes** (catalyst **1d**, see Supporting Information, Section D for more information). **1d** resulted in minimal conversion when applied to the benzoin condensation, which supports our hypothesis that the CDI is acting as a mask instead of a nucleophile in this system.

The stark change in reactivity between the latent and active states using our NHC-CDIs allowed us to perform a temporal control experiment in which pre-catalyst **1c** was switched between latency at 22 °C and rapid activation at 65 °C over multiple cycles (Figure 3, see Table S2 for tabulated data). Minimal conversion (≤1%) was observed during the first two "off" periods. At higher conversion, some activity remains during the "off" period and is accompanied by a seemingly "autocatalytic" effect wherein the rate of reaction speeds up.

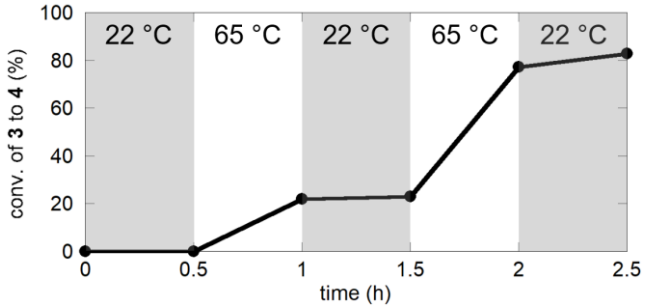


Figure 3. Temporal control over the benzoin condensation using **1c** as the pre-catalyst by modulating the reaction temperature.

While originally unexpected, we attribute both of these deviations to the formation of an adduct between the benzoin product **4** and the released CDI **2c**, which forms slowly over time.[64] After confirming that this side product was not a competent catalyst for the benzoin condensation (see Supporting Information, section F), we hypothesized that it has two effects: (1) at the 'activated' temperature (65 ˚C), it increases the reaction rate by pulling the NHC-CDI equilibrium towards dissociation via Le Chatelier's principle (i.e., increases [NHC]) and (2) at the 'deactivated' temperature (22 ˚C), it prevents full NHC capping, leading to the incomplete dormancy of the catalyst.[64] While this side reaction was not desired, it may provide an opportunity for more rapid activation upon the introduction of an alcohol additive.

To expand the scope of the NHC-CDI platform, we turned to the enal-aldehyde annulation[71,72] of *trans*-cinnamaldehyde (**5**) and *para*-chlorobenzaldehyde (**6**). This reaction proceeds through an NHC-derived homoenolate, another common organocatalytic intermediate,[73] to form a γ-lactone upon intramolecular ring closure. Qualitatively, the trend was the same as for the benzoin condensation (Figure 4, see Table S3 for tabulated data): the onset temperature of catalysis for **1c** is lower than **1b** (red triangles vs. blue circles). These results once again demonstrate the ability of the

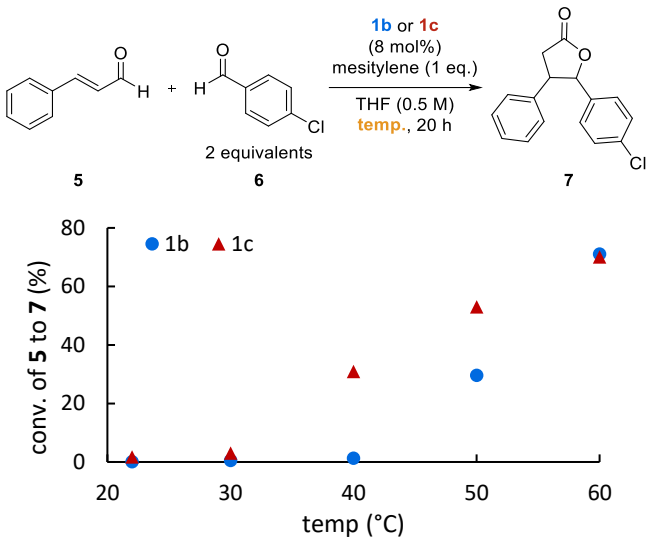


Figure 4. Lactone conversion in the enal-aldehyde annulation using **1b** or **1c** as pre-catalysts at different temperatures. Conversion was calculated via GC-FID vs. mesitylene as the internal standard.

NHC-CDI platform to tune the catalyst activation temperature with simple changes to the two substituent handles on the mask.

Surprisingly, control reactions showed that batch addition of free **IMes** at the beginning of the reaction performed worse than slow addition or slow deprotonation of a precursor salt (Table S4), perhaps due to a bimolecular catalyst deactivation pathway. In our system at 60 °C, batch addition of NHC-CDIs resulted in higher conversion (70% for adduct **1c**) than batch addition of free **IMes** (18%). We hypothesize that the reversibility of the NHC-CDI equilibrium keeps [NHC] low, which emulates slow addition and extends the catalyst lifetime for this reaction. This phenomenon could also explain the similar conversion to **7** for both adducts **1b** and **1c** at 60 °C: if the equilibrium [NHC] from **1c** is too high, it could lead to partial catalyst deactivation.

Both **1b** and **1c** appear to have a lower onset activation temperature for the annulation reaction compared to the benzoin condensation; however, the different reaction conditions must be considered. The enal-aldehyde annulation was done more dilute (0.5 M instead of 1.6 M) and for a longer time (20 h instead of 3 h) to disfavor side reactions.[72] When the benzoin condensation was run under the more dilute conditions using **1c** for 20 h, 87% conversion of **3** to **4** was observed at 40 °C (see Table S1, entry 11). This result demonstrates the importance of concentration and timescale on the NHC-CDI equilibrium.

In summary, a series of NHC-CDI adducts were used as competent pre-catalysts for NHC organocatalysis for the first time. In benzoin condensation, the *N*-alkyl-*N*′-aryl CDI adduct **1a** was latent at −34 °C but was too dynamic, such that catalysis was observed at 22 °C. The *N*,*N*′-diaryl CDI adducts **1b** and **1c** displayed the desired latent catalytic behavior at room temperature. Small perturbations to the CDI structure (i.e., phenyl vs. *para*-tolyl substituents) resulted in a >10 °C shift in the activation temperature of

the catalyst without changing the NHC structure, representing an important advance for metal-free NHC masks. The temperature release difference between adduct **1b** and **1c** was also observed in enal-aldehyde annulation, demonstrating the generality of this masking strategy. Additionally, the reversibility of this approach was highlighted by a temporal control experiment. Adduct formation between the benzoin product and the CDI mask resulted in an autocatalytic effect and incomplete reversibility at high conversions. Future work will focus on adjusting the mask structure to accommodate different systems with better temporal control and understanding the origins of adduct stability and catalyst release.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge at http://pubs.acs.org.
Kinetics data of CDI exchange experiments, control experiments, expanded data tables, experimental procedures, characterization data for new compounds, copies of NMR spectra (PDF)
CIF file for compound **1a** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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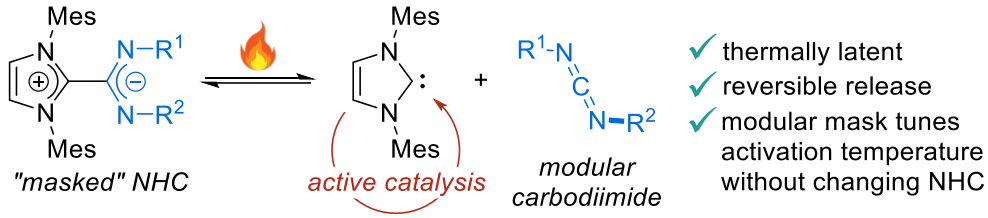
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