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1,4-Bis-Dipp/Mes-1,2,4-Triazolylidenes: Carbene Catalysts That Efficiently Overcome Steric Hindrance in the Redox Esterification of α- and β-Substituted α,β-Enals

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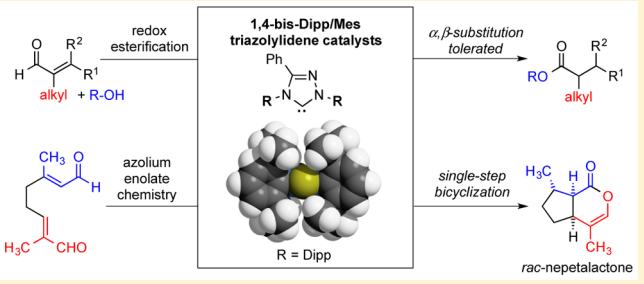
Supporting Information

ABSTRACT: As reported by Scheidt and Bode in 2005, sterically nonencumbered α,β-enals are readily converted to saturated esters in the presence of alcohols and N-heterocyclic carbene catalysts, e.g., benzimidazolylidenes or triazolylidenes. However, substituents at the α- or β-position of the α,β-enal substrate are typically not tolerated, thus severely limiting the substrate spectrum. On the basis of our earlier mechanistic studies, a set of *N*-Mes- or *N*-Dipp-substituted 1,2,4-triazolium salts were synthesized and evaluated as (pre)catalysts in the redox esterification of various α- or β-substituted enals. In particular the 1,4-bis-Mes/Dipp-1,2,4-triazolylidenes overcome the above limitations and efficiently catalyze the redox esterification of a whole series of α/β-substituted enals hitherto not amenable to NHC-catalyzed transformations. The synthetic value of 1,4-bis-Mes/Dipp-1,2,4-triazolylidenes is further demonstrated by the one-step bicyclization of 10-oxocitral to (racemic) nepetalactone in diastereomerically pure form.



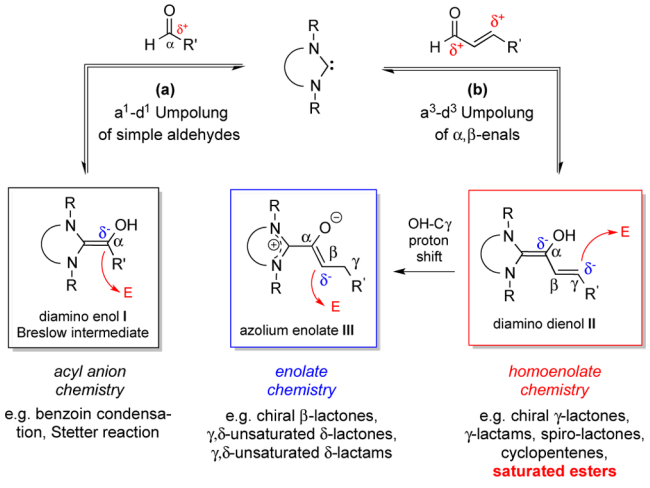
I. INTRODUCTION

N-Heterocyclic carbenes (NHCs) have emerged as highly efficient organocatalysts for a wide range of transformations.[1] The most intriguing use of NHCs is based on their ability to render the electrophilic carbonyl unit of aldehydes nucleophilic, thus converting them to acyl anion equivalents (a^1-d^1 umpolung to the Breslow intermediate **I**; Scheme 1a).[2] Important applications of a^1-d^1 umpolung are the benzoin condensation and the Stetter reaction.[3]

Beyond the generation of acyl anion equivalents, the "conjugate umpolung" of α,β-unsaturated aldehydes (a^3-d^3 umpolung), discovered by Bode and Glorius in 2004,[4] has recently become a most fascinating and proliferative field in NHC catalysis. In this process, the NHC catalyst and the enal substrate first combine to form diamino dienol **II** (Scheme 1b). In the latter, the β-position of the substrate α,β-unsaturated carbonyl compound (a^3) is rendered nucleophilic, too. Therefore, diamino dienols **II** can act as homoenolate equivalents (d^3) (Scheme 1b).[5] A subsequent OH−Cγ proton shift may convert **II** to azolium enolate **III** (Scheme 1b), an enolate equivalent (d^2).

Both the homoenolate and azolium enolate pathways have, in virtuosic manner, been exploited for the synthesis of complex target structures,[1b] in many cases in an enantioselective fashion.[6,7] Among the homoenolate reactions, the internal redox esterification of enals catalyzed by NHCs provides a new and fully atom-economical approach to saturated esters under redox-neutral conditions without the use of coupling reagents

Scheme 1. NHC-Catalyzed Umpolung of (a) Simple Aldehydes and (b) α,β-Enals



(Scheme 2).[8,9] Scheidt and Chan first reported the reaction conditions using a benzimidazolium-derived NHC (catalyst **30**; vide infra) in combination with excess phenol, effecting β-protonation/esterification of enals to form saturated esters in 56−90% yield.[8] Shortly thereafter, Bode and Sohn demon-

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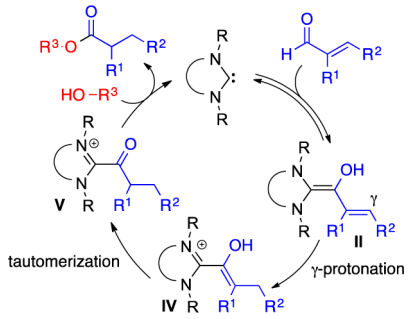
Scheme 2. Proposed Mechanism for the NHC-Catalyzed Redox Esterification of α,β-Enals



strated the use of a 2,4,6-trimethylphenyl (mesityl, Mes)-substituted triazolium salt as a highly effective catalyst for the redox esterification, with no additional proton source needed.[9] Mechanistically, the redox esterification of α,β-enals is believed to result from γ-protonation of diamino dienol **II** (Scheme 2) to give azolium enol **IV**, followed by tautomerization of the latter to acyl azolium cation **V**. Deacylation of the latter by the alcohol nucleophile furnishes the product ester and regenerates the NHC catalyst.

Inspection of the α,β-enal substrates employed reveals, however, that in *all* a^3-d^3 umpolung reactions, exclusively α-*unsubstituted* α,β-enals have found application, including NHC-catalyzed redox esterifications (i.e., R^1 = H in Scheme 2).[5] The only exception may be seen in α-methylcinnamic aldehyde.[4c,8a] This aldehyde was reported by Scheidt and Chan[8a] to be converted to the corresponding ester, but again proved recalcitrant under Bode's conditions.[9a] With this in mind, we engaged in a study aimed at (i) elucidation of the mechanistic reasons for the recalcitrance of α-substituted α,β-enals in redox esterifications, and (ii) the design, synthesis, and application of a new generation of NHC catalysts that overcomes the mechanistic hurdles. As the touchstone reaction, the redox esterification of α-substituted α,β-enals (e.g., hexahydro-α-methylcinnamic aldehyde) that are completely unreactive in the presence of known NHC catalysts was envisaged.

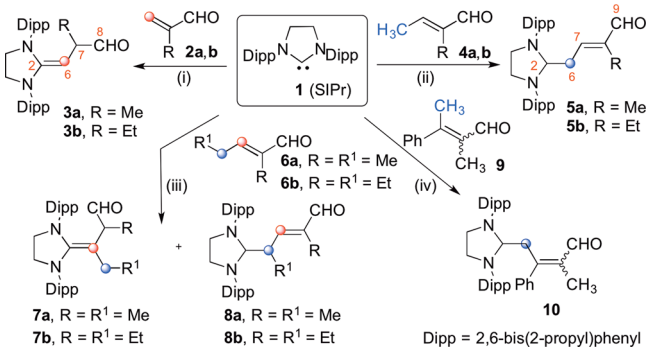
II. RESULTS AND DISCUSSION

II.1. Catalyst Design: The Importance of *N*-Mes/*N*-Dipp Substituents. Earlier studies by Bode and co-workers[9] had led to the conclusion that the formation of diamino dienol **II** from cinnamic aldehyde and the NHC catalyst is *irreversible*, thereby promoting the ester formation (R^1 = H, R^2 = Ph; Scheme 2). On the other hand, the analogous transformation of α-methylcinnamic aldehyde (R^1 = CH_3, R^2 = Ph) was assumed to be *reversible*, resulting in an inefficient overall process. The presence of an *N*-mesityl group on triazolium NHCs was found to be essential for reactions of α,β-enals involving the conjugated Breslow intermediate (diamino dienol **II**; Scheme 2).[5c,9] This "*N*-mesityl effect" was proposed to promote the formation of the key Breslow intermediate.

Our earlier work had supported the above assumptions in the sense that the imidazolidinylidene SIPr (**1**) forms a stable diamino dienol with cinnamic aldehyde that is amenable to X-ray crystallography.[10] In contrast, the formation of the analogous conjugated Breslow intermediate from α-methylcinnamic aldehyde was found to be reversible, and the latter diamino dienol readily tautomerized to the more stable azolium enolate (X-ray).[10,11] The solid-state structures of the Breslow intermediates point to a stabilizing dispersive effect[12,13] of the ancillary isopropyl groups of SIPr (**1**), presumably the molecular basis of the *N*-mesityl effect mentioned earlier.[5c,9] On the basis of these results, we sought to employ triazolylidenes carrying efficient dispersion energy donors (DEDs), such as 2,6-bis(2-propyl)phenyl (Dipp), to effect the problematic redox esterifications of α-substituted enals. We anticipated that the diamino dienol intermediates of type **II** (Scheme 2) would be stabilized by dispersion interactions as well, hence promoting the overall catalytic transformation.

II.2. Catalyst Design: Undesired Side Reactions of α-Substituted Enals with the Saturated N-Heterocyclic Carbene SIPr (1). In our NMR studies on the interaction of **1** with α,β-enals other than α-methylcinnamic aldehyde, we observed several reaction modes that do not afford the diamino dienol and thus no ester product [summarized in Scheme 3; see the Supporting Information (SI) for NMR data].

Scheme 3. Reaction of SIPr (1) with α-Substituted Enals in THF-d_8



^{1}H NMR monitoring at room temperature revealed that for methacrolein (**2a**) and ethacrolein (**2b**) as substrates, clean Michael addition to afford the corresponding deoxy-Breslow intermediates[14] **3a** and **3b** occurred [Scheme 3, (i); see the SI for the X-ray crystal structure of **3b**]. On the other hand, the interaction of SIPr with (*E*)-2-methyl-2-butenal (**4a**) afforded exclusively the formal γ-C−H insertion adduct **5a** [Scheme 3, (ii)]. The latter most likely results from allylic deprotonation of the enal by the NHC and subsequent recombination of the allyl anion with the imidazolidinium cation. Characteristic ^{1}H NMR signals of **5a** are a multiplet at δ = 2.43−2.41 ppm (2H, H6), a triplet at δ = 5.0 ppm ($^3J_{HH}$ = 5.0 Hz, 1H, H2), a triplet at δ = 5.88 ppm ($^3J_{HH}$ = 6.5 Hz, 1H, H7), and a singlet at δ = 8.78 ppm (1H, H9), and its ^{13}C NMR resonances appear at δ = 80.4 (C2), 35.8 (C6), 149.4 (C7), and 192.5 (C9) ppm. Similar NMR features for the formation of **5b** were observed when (*E*)-2-ethyl-2-butenal (**4b**) was exposed to **1**. It should be noted that the analogous reaction of α-unsubstituted 2-butenal [(*E*)-crotonaldehyde] with **1** gave exclusively the 1,2-addition adduct, the azolium enolate in this case.[10a]

The interaction of enals **6** with SIPr (**1**) gave a mixture of **7** (Michael addition) and **8** (formal γ-C−H insertion) [Scheme 3, (iii)]. With (*E*)-2-methyl-2-pentenal (**6a**), **7a** and **8a** were obtained in a ratio of 5:3. When (*E*)-2-ethyl-2-hexenal (**6b**) was reacted with **1**, **7b** was obtained along with just a trace amount of **8b**. Unexpectedly, the reaction of **1** with **9**, the β-methyl derivative of α-methylcinnamic aldehyde (used as the pure *E* isomer or an *E*/*Z* mixture), gave only the formal C−H insertion adduct **10** [Scheme 3, (iv); see the SI for the X-ray

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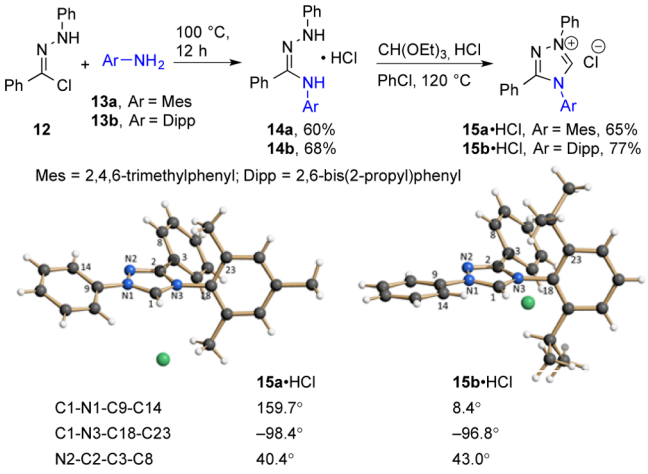
analysis of **10**]. In contrast to the reactivity of α-methylcinnamic aldehyde,[10a] no 1,2-addition affording the diamino dienol/azolium enolate was observed for enal **9**.

The above-mentioned observations reveal a major competitive reaction pathway: when the addition of the NHC catalyst to the enal's carbonyl C atom is sterically impeded, allylic proton abstraction may occur. To suppress this side reaction, low-basicity NHCs must be employed.[15] 1,2,4-Triazol-5-ylidenes are significantly less basic (aqueous pK_a ~ 16.5−18.5)[15a] than imidazolidin-2-ylidenes such as SIPr [aqueous pK_a of **1** ≈ 21.5].[15b] Additionally, in redox esterification, 1,2,4-triazol-5-ylidenes had previously been shown to be catalytically superior to imidazol-2-ylidenes and thiazol-2-ylidenes.[9a] Accordingly, we focused on the synthesis of new NHCs based on the 1,2,4-triazole core by exchanging the *N*-phenyl substituents of the well-known Enders−Teles carbene **11**[16] for Dipp or Mes groups. It should be noted that on the basis of calculations, the additional phenyl group at the 3-position of **11** is believed to support its higher Lewis basicity, and hence its higher reactivity, compared with 3-unsubstituted analogues.[17]

II.3. Synthesis of Mono-Mes/Dipp-1,2,4-Triazolium Salts. For the later comparison of reactivities, we aimed at synthesizing a series of mono/bis-Mes/Dipp- and bis-Ipp/BPh-substituted triazolium salts [Ipp = 2-(2-propyl)phenyl; BPh = *o*-biphenylyl]. Condensation of *N*-phenylbenzohydrazonoyl chloride (**12**)[18] with Mes/Dipp-amines **13** gave the desired isomers of hydrazoneamides **14** (Scheme 4). After ring closure

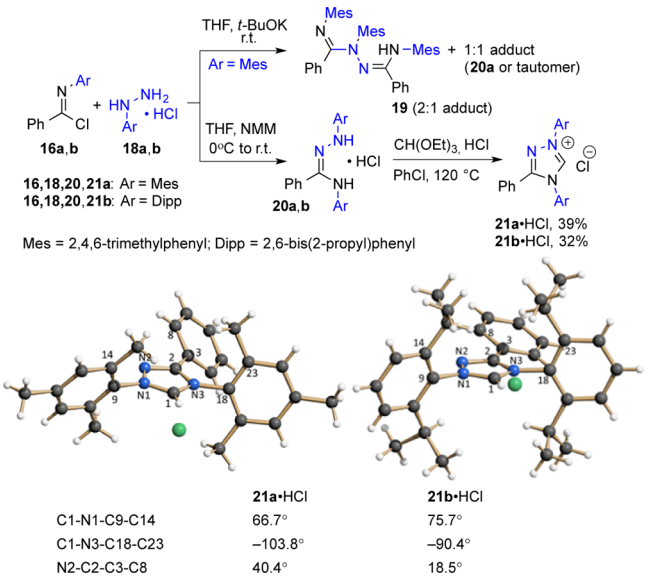
Scheme 4. Synthesis and X-ray Crystal Structures of Mono-Mes/Dipp-1,2,4-Triazolium Salts 15a·HCl and 15b·HCl



with triethyl orthoformate,[19] the desired triazolium salts **15a**·HCl and **15b**·HCl were obtained in good yields after precipitation from ethyl acetate. Recrystallization from hot ethyl acetate and dichloromethane (3:1) afforded crystalline samples of **15a**·HCl and **15b**·HCl suitable for X-ray structural analysis. The two crystal structures are similar in the sense that the phenyl ring at N1 is virtually coplanar with the triazolium ring, while the phenyl group at C2 is twisted out of the plane. Most interestingly, the Mes/Dipp group at N3 is almost perpendicular to the triazolium ring, with C1−N3−C18−C23 dihedral angles of −98.4° and −96.8° for **15a**·HCl and **15b**·HCl, respectively.

II.4. Synthesis of Bis-Mes/Dipp-1,2,4-Triazolium Salts. After the successful preparation of the mono-Mes/Dipp-substituted triazolium salts **15a** and **15b**, we further explored the synthesis of the bis-Mes/Dipp-substituted precatalysts (Scheme 5). The key step was the coupling reaction of the

Scheme 5. Synthesis and X-ray Crystal Structures of Bis-Mes/Dipp-1,2,4-Triazolium Salts 21a·HCl and 21b·HCl



hydrochlorides **18a** and **18b**[20] (of the corresponding Mes/Dipp-hydrazines **17a** and **17b**) with the corresponding imidoyl chloride **16**.[21] We found that the addition of mesitylhydrazine (**17a**, prepared *ex situ* from the salt **18a** by treatment with *t*BuOK) to a solution of *N*-mesityl imidoyl chloride **16a** in tetrahydrofuran (THF) at room temperature resulted in the formation of **19**, a 2:1 adduct, as the major product. The structure of **19** was unambiguously established by X-ray analysis (see the SI).

Gratifyingly, upon modification of the reaction conditions [*in situ* treatment of hydrazinium salts **18** with *N*-methylmorpholine (NMM), 0 °C reaction temperature], the formation of the desired hydrazoneamides **20** was achieved, which could be used in the next step without prior purification. The final ring closure of **20a** and **20b** was effected by treatment with triethyl orthoformate, furnishing the desired bis-Mes/Dipp-substituted precatalysts **21a**·HCl and **21b**·HCl, respectively, in moderate yields. The X-ray crystal structures of **21a**·HCl and **21b**·HCl are shown in Scheme 5 (bottom). In the solid state, the phenyl group at C2 in both **21a**·HCl and **21b**·HCl is twisted out of the plane of the triazolium ring, with N2−C2−C3−C8 dihedral angles of 40.4° and 18.7°, respectively. The two Mes/Dipp groups at N1 and N3 of the heterocyclic ring (C1−N1−C9−C14 and C1−N3−C18−C23 dihedral angles) in **21a**·HCl and **21b**·HCl are arranged in an almost perpendicular fashion, the two Dipp groups of **21b**·HCl more so than the two mesityl groups of **21a**·HCl. Notably, one of the Dipp groups of **21b**·HCl is perfectly arranged perpendicular to the triazolium ring (C1−N3−C18−C23 dihedral angle = −90.4°).

II.5. Synthesis of Bis-Ipp/BPh-1,2,4-Triazolium Salts. Our third line of syntheses aimed at the bis-Ipp/BPh-1,2,4-

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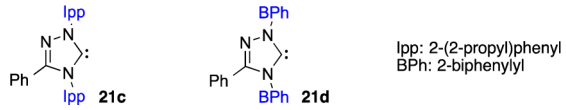
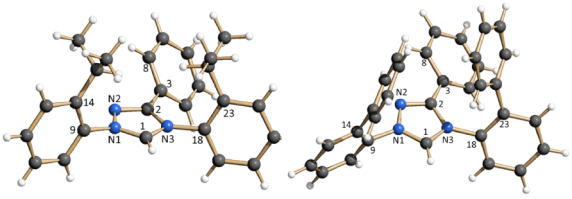
triazolium carbenes **21c** and **21d**. The Ipp/BPh groups were hoped to still induce a perpendicular arrangement of the *N*-



substituents relative to the triazolium core. At the same time, they were expected to have a weaker shielding effect with regard to the reactive carbene site. The bis-Ipp/BPh-triazolium salts of **21c** and **21d** were prepared by a procedure analogous to the one summarized in Scheme 5 (see the SI for complete experimental details). Attempts to crystallize the hydrochlorides of **21c** and **21d** were unsuccessful. However, upon anion exchange to the corresponding tetraphenylborates, we obtained crystalline samples of **21c**·$HBPh_4$ and **21d**·$HBPh_4$ suitable for X-ray structural analysis (Figure 1).



	21c•$HBPh_4$	**21d**•$HBPh_4$
C1-N1-C9-C14	89.6°	87.5° (74.0°)
C1-N3-C18-C23	–98.7°	–114.8 (–97.7°)
N2-C2-C3-C8	43.3°	24.0° (38.3°)

Figure 1. X-ray crystal structures of **21c**·$HBPh_4$ and **21d**·$HBPh_4$ (two independent molecules per unit cell; dihedral angles of the second form are given in parentheses). The tetraphenylborate anions have been omitted for clarity.

In fact, both *N*-substituents, especially those of **21c**·$HBPh_4$, are almost perpendicular to the heterocyclic core, particularly at N1 and less pronounced at N3. In the case of **21d**·$HBPh_4$, we found two independent molecules per unit cell. It is striking that both ortho substituents of the aromatic substituents at N1 and N3 point to the same side of the triazolium ring. In the case of **21c**·$HBPh_4$, this conformation exists also in $CDCl_3$ solution, as evidenced by nuclear Overhauser effect (NOE) signals between the two *i*Pr-groups (see the SI for NMR data).

II.6. Spectroscopic Properties, X-ray Crystal Structures, and Catalytic Activities of the Free Carbenes. For NMR spectroscopic analysis (THF-d_8), the free carbenes **15a,b** and **21a–d** were generated by *in situ* deprotonation of the corresponding triazolium salts with *t*BuOK, or catalytic *t*BuOK together with NaH or KH. The carbene C atoms of **15a**, **15b**, **21a**, **21b**, **21c**, and **21d** resonate at δ = 216.4, 216.7, 218.1, 219.0, 217.7, and 218.2 ppm, respectively. Their ^{13}C NMR signals are thus in a range similar to that for triphenyl triazolylidene **11**, the carbene C atom of which has its resonance at δ = 214.8 ppm.[22]

Single crystals of the free carbenes **21a** and **21b** suitable for X-ray structural analysis were obtained by crystallization from a 3:1 mixture of *n*-pentane and THF. The molecular structure of **21b** is shown in Figure 2 (see the SI for the structure of **21a**). Comparison of the solid-state structures of the carbene **21b** (two independent molecules per unit cell) and the azolium salt **21b**·HCl (cf. Scheme 5) revealed significant differences. The bond angle at the carbene carbon C1 in **21b** is significantly smaller than that in **21b**·HCl. For **21b**, the N1–C1–N3 angle

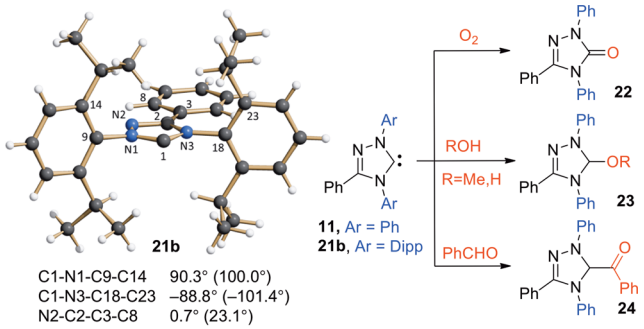


Figure 2. (left) X-ray crystal structure of bis-Dipp-1,2,4-triazolylidene **21b** (two independent molecules per unit cell; bond angles of the second form are given in parentheses). (right) Comparison of the reactivities of 1,2,4-triazolylidenes **11** and **21b**.

of 100.6° (99.4°) is typical for singlet carbenes,[23] whereas the N1–C1–N3 angle amounts to 106.9° in **21b**·HCl. The C1–N1 and C1–N3 bonds in **21b** are elongated to 1.35–1.38 Å from the values of 1.32–1.33 Å found in the triazolium salt **21b**·HCl. However, the N1–C9 and N3–C18 bond lengths (1.442–1.444 Å) are shorter than the corresponding bond lengths in **21b**·HCl (1.459–1.460 Å). Upon moving from the triazolium salt **21b**·HCl to the carbene **21b**, the largest structural changes occur around the carbene center of **21b**. These changes reflect diminished π delocalization in **21b** compared with **21b**·HCl. In the carbene **21b**, the phenyl group at C2 is virtually coplanar with the heterocyclic ring, while the Dipp groups at N1 and N3 are perpendicular to the plane of the heterocyclic ring.

We next examined the stability of the new triazolylidenes **15** and **21** toward MeOH. At room temperature, the Enders–Teles carbene **11** inserts into the O–H bond within minutes and affords the methanol adduct **23** (R = Me) quantitatively (Figure 2). In contrast, mono-Mes-substituted **15a** and mono-Dipp-substituted **15b** reached equilibrium after ca. 1 day, with the methanol adducts being formed in ca. 90% and 67% yield, respectively. Similarly, equilibrium was reached at ca. 60% conversion for bis-Ipp-substituted **21c**. In contrast, bis-BPh-substituted carbene **21d** was completely converted to the methanol adduct within 1 h. Remarkably, for the bis-Mes- and bis-Dipp-substituted carbenes **21a** and **21b**, no reaction with methanol could be observed over 5 days. Furthermore, solutions of **21b** showed no reaction with atmospheric oxygen, water, or benzaldehyde over 5 days, while triphenyl triazolylidene **11** reacts instantaneously with water (to afford **23** with R = H) and oxygen (to give urea **22**) and adds stoichiometric benzaldehyde (to furnish ketone **24**) (Figure 2).[16a,22] These results clearly indicate strong shielding of the carbene center by the two Mes/Dipp groups. It should be noted, however, that **21b** effected the condensation of more reactive aldehydes, such as propionaldehyde, 3-phenylpropionaldehyde, and 2,4-bis(trifluoromethyl)benzaldehyde, to give benzoin products.

II.7. Redox Esterification of α-Substituted Enals: Identification of Suitable NHC Catalysts. With the new triazolium precatalysts in hand, we proceeded to investigate their activity in the redox esterification of *α-substituted α,β-*unsaturated aldehydes. As reported by Scheidt and Chan,[8a] the redox esterification of α-methylcinnamic aldehyde could be performed under NHC catalysis using benzimidazolium

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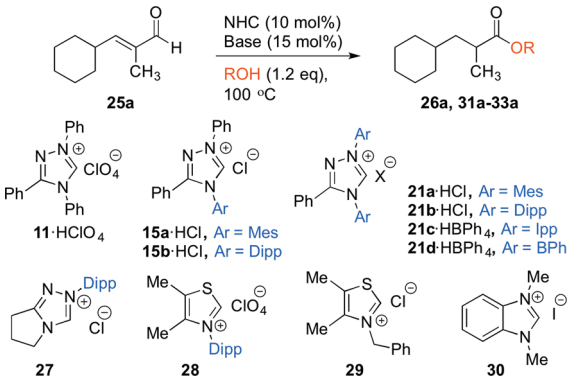
precatalyst **30**. More demanding substrates, such as hexahydro-α-methylcinnamic aldehyde (**25a**) or enals **25e** and **25j** (see Table 2), gave no reaction at all under the conditions described by Scheidt and Chan. We chose **25a** as the model substrate for our study, and various NHCs were tested under standard conditions [10 mol % NHC, 15 mol % base, and 1.2 equiv of alcohol (ROH) at 100 °C]. The results are summarized in Table 1.

Table 1. Optimization of the Reaction Conditions for Redox Esterification



entry	catalyst	base	ROH	time [h]	relative yield [%][a]
1	**11**·$HClO_4$	DIPEA	BnOH	40	0[b]
2	**15a**·HCl	DIPEA	BnOH	40	**26a**, 33
3	**15b**·HCl	DIPEA	BnOH	40	**26a**, 60
4	**21a**·HCl	DIPEA	BnOH	40	**26a**, 75
5	**21b**·HCl	DIPEA	BnOH	40	**26a**, **97**
6	**21c**·$HBPh_4$	DIPEA	BnOH	40	**26a**, 18
7	**21d**·$HBPh_4$	DIPEA	BnOH	40	**26a**, 20
8	**27**	DIPEA	BnOH	40	**26a**, 15
9	**28**	DIPEA	BnOH	40	**26a**, 51
10	**29**	DIPEA	BnOH	40	0[b]
11	**30**	DIPEA	BnOH	40	0[b]
12[c]	**21b**·HCl	DIPEA	BnOH	120	**26a**, 97
13	**21b**·HCl	DBU	BnOH	30	**26a**, trace[b]
14	**21b**·HCl	Et_3N	BnOH	40	**26a**, 90
15	**21b**·HCl	NMM	BnOH	40	**26a**, 33
16	**21b**·HCl	DIPEA	MeOH	30	**31a**, 90
17	**21b**·HCl	DIPEA	EtOH	30	**32a**, 90
18	**21b**·HCl	DIPEA	H_2O	30	**33a**, 90

[a]Determined by ^1H NMR analysis of the crude reaction mixtures. [b]Determined by GC–MS. [c]5 mol % catalyst and 8 mol % DIPEA were used.

To our delight, all of the new triazolium-based catalysts **15a**, **15b**, and **21a–d** provided the desired saturated ester **26a**, while the parent triphenyl triazolium catalyst **11** gave no conversion at all (entries 1–7). Among the new triazolium precatalysts, the bis-Dipp salt **21b**·HCl gave the best results (entry 5). It can be seen clearly that the reactivity of the *N*-Dipp-substituted azolium is superior to that of its mesityl analogue [**21b**·HCl > **21a**·HCl (entry 5 vs 4) and **15b**·HCl > **15a**·HCl (entry 3 vs 2)]. Furthermore, triazoles with twofold *N*-Dipp/Mes substitution are more efficient than their mono-*N*-Dipp/Mes-substituted analogues [**21b**·HCl > **15b**·HCl (entry 5 vs 3) and **21a**·HCl > **15a**·HCl (entry 4 vs 2)]. On the other hand, the azolium salts with twofold mono-ortho substitution (**21c**·$HBPh_4$ and **21d**·$HBPh_4$) were catalytically less active than the mono-*N*-Mes-substituted salt **15a**·HCl (entries 6 and 7 vs entry 2). This is in line with previous reports that reactions of α,β-enals are more effectively catalyzed by NHCs carrying ortho,ortho′-disubstituted aromatic groups on the triazolium ring (the "mesityl effect").[5]

We furthermore examined **27**, the *N*-Dipp analogue of the *N*-Mes catalyst described by Bode et al.[9] (see the SI for the synthesis and X-ray crystal structure of **27**), and *N*-Dipp-substituted thiazolium salt **28**, previously described by Glorius and co-workers.[24] Thiazolium salt **28** was found to be more effective than **27** (entry 9 vs 8) but less reactive than our mono- and bis-Dipp-substituted precatalysts **15b**·HCl and **21b**·HCl. With **28**, we observed the pronounced formation of unsaturated ester (~17%) as a byproduct. It should be noted that thiazolium **29**, which was successfully applied to the redox esterification of α,β-epoxy aldehydes,[25] as well as benzimidazolium **30**[8a] gave no product formation with enal **25a** as the substrate (entries 10 and 11).

Lowering the loading of the precatalyst **21b**·HCl to 5 mol % did not affect the excellent yield of **26a** obtained, but a longer reaction time was necessary (entry 12). We also examined the effect of different bases. Et_3N proved to be almost as effective as *N*,*N*-diisopropylethylamine (DIPEA) (entry 14), but 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to trace amounts of product only (entry 13). Much lower reaction rates resulted from the use of weaker bases, such as NMM (entry 15). This result is consistent with observations by Bode and Sohn[9a] that DIPEA and Et_3N are the most effective bases, presumably acting as proton shuttles. Variation of the alcohol component from benzyl alcohol to methanol or ethanol resulted in similarly high ester yields (entries 16 and 17). Remarkably, even water can serve as the nucleophilic component, affording the carboxylic acid (entry 18).

II.8. Substrate Scope of the Bis-Dipp-1,2,4-Triazolium (Pre)catalyst 21b·HCl. With the newly developed catalytic system [bis-Dipp triazolium salt **21b**·HCl (5–10 mol %), DIPEA (1.5 equiv relative to **21b**·HCl)] in hand, we set out to study the substrate scope with regard to various α-substituted enals (Table 2). To our delight, the redox esterification of a variety of α-methyl-, α-ethyl-, and even α-isopropyl-substituted enals proceeded smoothly under our catalytic conditions, affording the corresponding esters **26a–l** in very good isolated yields of 70–82%. Notably, only with the enals **25i** and **25m** as substrates were trace amounts of unsaturated ester detected as a byproduct. In the case of α-fluoroenal **25m**, dehydrofluorinated product was obtained together with the saturated fluoroester **26m**. For the β,β-disubstituted enals **25n–q**, a 5 mol % loading of **21b**·HCl was sufficient to complete the redox esterification within 10–12 h. In line with this result, the transformation of the less hindered β-monosubstituted enals **25r–v** proceeded even more rapidly, reaching completion within 6–8 h. It should be noted that **25p** was previously reported by Scheidt and Chan[8a] to be recalcitrant toward redox esterification under their conditions with benzimidazole **30** as the catalyst.

Under our standard conditions, the α,β,β-trisubstituted enals **9** and **25w–y** remained unchanged and did not yield the desired ester products, most likely because of excessive steric hindrance. Interestingly, no formal γ-C–H insertion occurred as a side reaction, as was the case with SIPr (**1**) as the carbene (cf. Scheme 3). We attribute this result to the lower basicity of **21b** compared with **1**. In the cases of the α-methylene aldehydes **25aa** and **25ab**, no ester formation was observed. As ESI-MS analysis of the reaction mixtures indicated the

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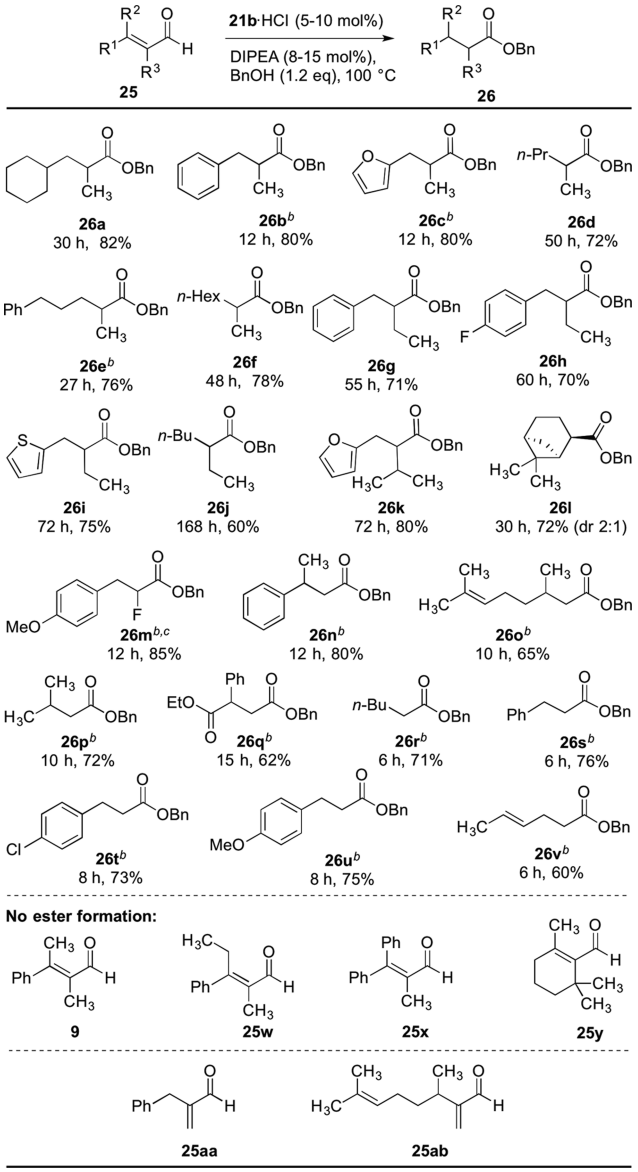
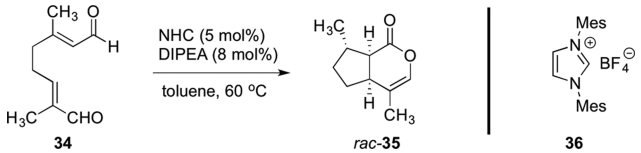
Table 2. Substrate Scope of the (Pre)catalyst 21b·HCl[a]



[a]10 mol % catalyst and 15 mol % DIPEA were used, unless otherwise noted. Isolated yields are given. [b]5 mol % catalyst and 8 mol % DIPEA were used. [c]A 1:1 mixture of **26m** and dehydrofluorinated cinnamic ester was obtained.

Table 3. Catalyst Screening for the One-Step Synthesis of *rac*-Nepetalactone (*rac*-35)



entry	catalyst	t [h]	yield [%][a]
1	**11**·$HClO_4$	20	0
2[b]	**11**	12	0
3	**15b**·HCl	18	34
4	**21a**·HCl	6	66 (60)
5	**21b**·HCl	6	60 (55)
6[c]	**21b**·HCl	50	63
7	**21c**·$HBPh_4$	24	trace
8	**21d**·$HBPh_4$	24	trace
9	**27**	20	0
10	**28**	12	0
11	**36**	24	0

[a]The reactions were performed until completion, and the product yields were determined by GC using dodecane as an internal standard. Isolated yields are shown in parentheses. [b]10 mol % phenol was added. [c]No base was added.

formation of 1:1 adducts of the carbene catalyst with the substrates, we assume that Michael addition to the deoxy-Breslow intermediates had occurred [cf. Scheme 3 for the analogous cases of methacrolein (**2a**) and ethacrolein (**2b**)].

II.9. Application of NHC Catalysis to the One-Step Synthesis of Nepetalactone (*rac*-35). The naturally occurring monoterpene nepetalactone (**35**) (Table 3) was first isolated in 1941 by distillation from catnip oil.[26] Recently, it has been used as the starting material in the synthesis of biologically highly active Englerin A by Christmann and co-workers.[27] A literature survey revealed a few enantioselective preparations of nepetalactone from 10-oxocitral (**34**) or citronellal requiring several synthetic steps.[28] Here we disclose the first one-step synthesis of nepetalactone from **34** by NHC catalysis.

As shown in Table 3, the bis-Mes/Dipp-1,2,4-triazolium salts **21a**·HCl and **21b**·HCl were similarly effective catalysts for the bicyclization of linear **34** to give *rac*-**35** (entries 4 and 5). The bis-Mes-substituted (pre)catalyst **21a**·HCl proved somewhat superior, affording *rac*-**35** in 60% isolated yield (entry 4). Remarkably, the product *rac*-**35** was obtained as the single diastereomer with a cis junction of the five-membered rings and an exo orientation of the methyl substituent, as shown in Table 3. This diastereomer has previously been shown to be the thermodynamically most stable one.[29] The mono-Dipp-substituted triazolium salt **15b**·HCl gave a moderate yield (entry 3). In contrast, both triphenyl triazolylidene **11** and its perchlorate salt, the mono-Dipp-substituted precursors **27** and **28** (see Table 1 for structures), and IMes (**36**) were catalytically inactive (entries 1, 2, and 9−11). It is worthy of note that the conversion of **34** to *rac*-**35** also proceeded when triazolium salt **21b**·HCl was used in the absence of base (compare entries 5 and 6), albeit at a much lower rate.[30]

The mechanism proposed for the formation of nepatalactone by NHC catalysis is shown in Scheme 6. First, deprotonation of triazolium salt **21a,b**·HCl by the base generates the carbene **21a,b**. The sterically less hindered enal function of **34** is first attacked by the nucleophilic carbene **21a,b**, furnishing diamino dienol **II**. Intra- or intermolecular proton transfer to the γ-position of **II** provides azolium enolate **III**, which is now nucleophilic at the β-position. Subsequent intramolecular Michael addition of the latter enolate **III** to the α-methyl enal generates acyl azolium intermediate **V**. Finally, intramolecular attack of the enolate oxygen atom of **V** at the carbonyl group effects the ring closure to form nepetalactone and regenerates the carbene catalyst **21a,b**.

III. CONCLUSIONS

On the basis of the results of our mechanistic studies, we have designed and synthesized 1,2,4-triazolium salts and their corresponding triazolylidene carbenes carrying mesityl (Mes) and 2,6-bis(2-propyl)phenyl (Dipp) groups at N1 and N4. These novel N-heterocyclic carbenes efficiently catalyze the

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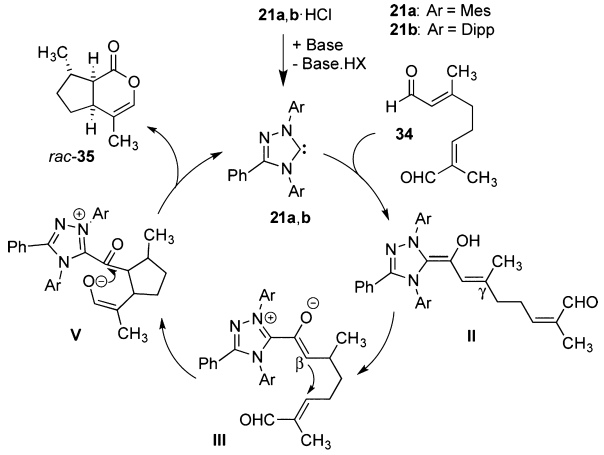
Scheme 6. Proposed Mechanism for the One-Step Synthesis of Nepetalactone



redox esterification of α- and β-substituted α,β-enals hitherto recalcitrant to this type of transformation. We interpret the superior catalytic activity of this new class of NHCs to result from (i) enhanced formation of the Breslow intermediate due to stabilizing interactions with the dipersion energy donors at N1 and N4 and (ii) their superior stability under the reaction conditions. Computational studies addressing, inter alia, the dispersive effects of Mes/Dipp substitution will be published elsewhere. Overall, the bis-Mes/Dipp-1,2,4-triazolium salts **21a**·HCl and **21b**·HCl have emerged from our study as novel NHC (pre)catalysts with significant potential for other, thus far impossible, umpolung reactions of α- or β-substituted α,β-enals. Work addressing the latter aspect is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11796.

Synthesis of all new triazolium salts; catalytic redox esterification of enals; one-step synthesis of *rac*-**35**; 1D and 2D NMR spectra of the products resulting from reactions of **1** and α-alkyl-substituted enals; and spectral data and X-ray data for **3b**, **10**, **15a**·HCl, **15b**·HCl, **19**, **21a**·HCl, **21b**·HCl, **21c**·$HBPh_4$, **21d**·$HBPh_4$, **27**, **21b**, and **21a** (PDF)

Crystallographic data in CIF format (ZIP)[31]

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Author Contributions

†J.-M.N.: X-ray crystallography.

Author Contributions

‡N.E.S.: NMR spectroscopy.

Notes

The authors declare no competing financial interest.

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