doi.org/10.1002/adsc.202300857

Advanced Synthesis & Catalysis

*Very Important Publication*

# Conjugate Aminocyclization Catalyzed by a Bismuthinidene

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Manuscript received: August 7, 2023; Revised manuscript received: September 21, 2023;
Version of record online: October 24, 2023

*Dedicated to Prof. Miquel A. Pericàs*

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202300857

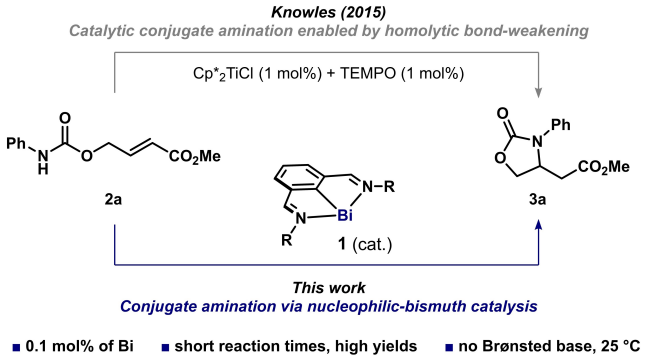


**Abstract:** We disclose how an *N*,*C*,*N*-bismuthinidene is able to promote an intramolecular conjugate amination that affords cyclic carbamates in 91–97% yields. The reaction proceeds at room temperature in short reaction times, requiring a remarkably low loading of a bismuth(I) complex (0.1 mol%) without the need of an additional Brønsted base. Preliminary mechanistic studies suggest that the reaction takes place through a polar pathway involving the conjugate addition of the nucleophilic bismuthinidene, followed by an intramolecular aza-Michael reaction.

**Keywords:** bismuth; cyclization; pnictogens; conjugate addition; nucleophilic catalysis

Traditionally, homogeneous bismuth catalysis has relied almost exclusively on the soft Lewis-acid properties of bismuth(III) complexes, which have been employed for the activation of π-bonds, benzylic alcohols or carbonyl compounds.[1] Recent years have witnessed the ability of bismuth to undergo one- and two-electron redox processes which can be valuable in organic synthesis.[2] This led to the emergence of a variety of catalytic platforms based on the Bi(I/III),[3] Bi(I/II/III),[4] and Bi(III/V)[5] redox manifolds, which solidify the capabilities of this heavy pnictogen to mimic and complement the reactivity of transition metals.[6] Of particular interest is the reactivity of *N*,*C*,*N*-bismuthinidenes such as **1**, originally developed by Dostál and co-workers.[7] These complexes have the ability to readily undergo oxidative processes (through both two-electron or single electron-transfer pathways), allowing the activation of organic electrophiles for eventual catalysis.[3,4,8] This behavior is the result of the reducing and nucleophilic nature of these low-valent bismuth complexes.

Within the broad context of nucleophilic organocatalysis,[9] trialkylphosphines have been used extensively in the activation of Michael-acceptor systems via conjugate addition,[10] emerging from landmark discoveries such as the Rauhut-Currier dimerization,[11] or the Morita-Baylis-Hillman reaction.[12] However, as a result of the low-energy $6s^2$ lone pair in organobismuth(III) compounds, bismuth has been largely overlooked in the context of nucleophilic or Lewis-base catalysis. In contrast, the analogous nucleophilic character of bismuth(I) complexes in comparison to phosphorus(III) compounds prompted us to explore the activity of *N*,*C*,*N*-bismuthinidene **1** as nucleophilic catalyst, specifically to activate α,β-unsaturated carbonyl compounds. In 2015, Knowles and co-workers reported that substrates such as **2a** could be activated via bond-weakening of the N–H bond, by combining catalytic amounts of $Cp^*_2Ti^{III}Cl$ and TEMPO (Scheme 1, top).[13] This resulted in a Brønsted base-free conjugate aminocyclization reaction,[13,14] which occurs under the aforementioned conditions via proton-coupled electron transfer. Inspired by this seminal report, we hypothesized that an alternative activation mode for the same type of substrate could be achievable via conjugate



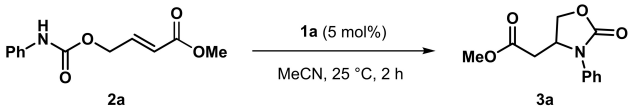

**Scheme 1.** Conjugate aminocyclizations: bond-weakening catalysis (top) vs conjugate amination catalyzed by nucleophilic bismuth(I) (this work, bottom).

addition of nucleophilic pnictogen compounds, such as bismuthinidene complexes (Scheme 1, bottom).

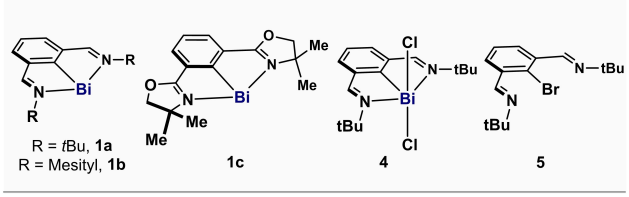
We prepared substrates **2** in a modular manner by reaction of different δ-hydroxy-α-β-unsaturated carbonyl compounds with aryl isocyanates in the presence of $NEt_3$ (see SI for details). We found that **2a** reacts smoothly in the presence of 5 mol% of *N*,*C*,*N*-bismuthinidene **1a** to afford cyclic product **3a** in almost quantitative yield at 25 °C (93% isolated product at 0.5 mmol scale). Other bismuthinidenes such as **1b** and **1c** delivered the product with a similar level of efficiency (Table 1, entries 2–3).[8] Remarkably, very small catalyst loadings (down to 0.1 mol% of **1a**) led to the formation of the desired product in short reaction times, at room temperature and without requirement of a Brønsted base (Table 1, entries 5–6). We confirmed that the presence of the bismuth(I) complex was required for the reaction to proceed under these conditions (entry 4). We also performed experiments where the Bi(I) was substituted by a variety of weak bases (entry 9), Lewis acids (entry 10) and single-electron reductants (entry 11); yet, no conversion of the starting material was observed. Importantly, the corresponding *N*,*C*,*N*-bismuth(III) dichloride complex (**4**, entry 7) and the Bi-free *N*,*C*,*N* ligand precursor (**5**, entry 8) did not display any catalytic activity. At this point, we explored the catalytic performance of several phosphines (entries 12–13). Whereas less nucleophilic $PPh_3$ or JohnPhos were unreactive, 20 mol% of more electron rich $PCy_3$ allowed full conversion of **2a** to **3a** in 2 h. This result points to a polar process based on the nucleophilicity of either the phosphine or the Bi(I) complex (vide infra).

After this survey of conditions, we explored the generality of the transformation using 1 mol% of **1a** in MeCN at 25 °C (Scheme 2). First, we evaluated the range of electron-withdrawing groups that could be accommodated in the Michael-acceptor system. The reaction proceeded smoothly using esters (**3a**–**b**, **3i**), ketones (**3c**), nitriles (**3d**) or amides (**3e**). We could

**Table 1.** Optimization and control experiments.



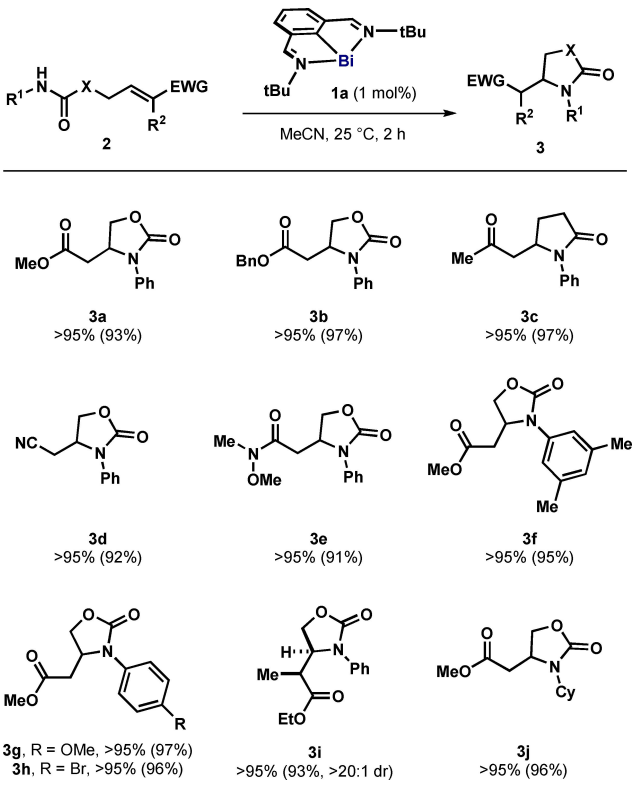

| Entry | Deviation from standard conditions[a] | Yield of **3a** |
|---|---|---|
| 1 | none | >95% (93%) |
| 2 | **1b** (5 mol%) instead of **1a** | >95% |
| 3 | **1c** (5 mol%) instead of **1a** | 94% |
| 4 | without **1a**, 16 h | n/d |
| 5 | 1 mol% of **1a**, 15 min | >95% |
| 6 | 0.1 mol% of **1a**, 1 h | >95% |
| 7 | **4** (5 mol%) instead of **1a** | n/d |
| 8 | **5** (5 mol%) instead of **1a** | n/d |
| 9 | Weak bases (50 mol%) instead of **1a**: $NEt_3$ *or* AcONa, 16 h | n/d[b] |
| 10 | $ZnBr_2$, CuI, $InCl_3$, $FeBr_3$, $AgF_2$,16 h instead of **1a** | n/d[b] |
| 11 | Zn dust (50 mol%) instead of **1a**, 16 h | n/d |
| 12 | $PPh_3$ (20 mol%) or JohnPhos (10 mol%) instead of **1a**, 16 h | n/d |
| 13 | $PCy_3$ (20 mol%) instead of **1a** | >95% |



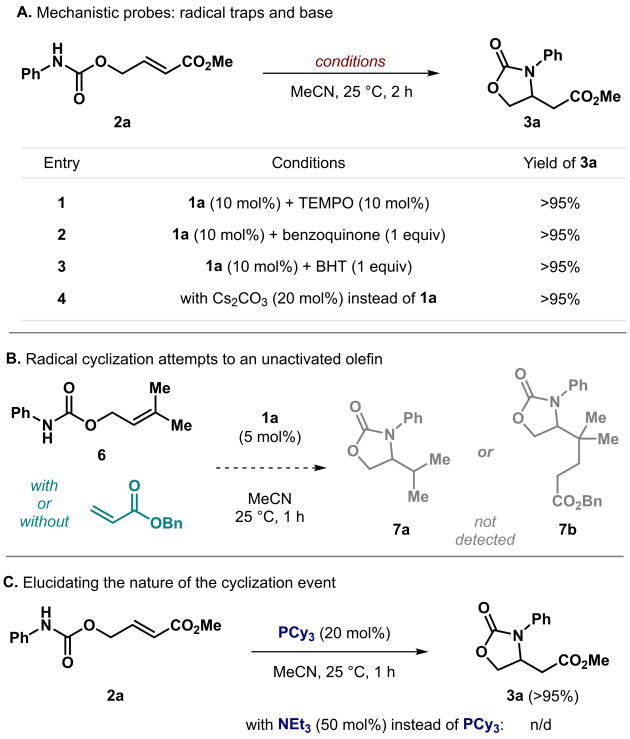

[a] Standard conditions: 0.1 mmol of **2a**, 5 mol% of **1a** in MeCN (0.1 M) for 16 h at 25 °C. Yields determined by $^1$H NMR using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in parenthesis.
[b] Reactions tested using either MeCN or THF as solvent (see SI for details).

also decorate the aryl group connected to the N atom with various substituents, such as 4-bromophenyl or 4-methoxyphenyl, giving products **3f**–**h** successfully. More electron-poor aromatic moieties such as pentafluorophenyl led to spontaneous cyclization during the preparation of the corresponding substrate **2**, presumably due to the significantly increased acidity of the N–H bond (see SI for details). We also show that substrates bearing an alkyl in place of an aryl group in the N atom were amenable to cyclization under the optimized conditions (**3j**). Reactive groups that can potentially act as handle for further functionalization were also tolerated, such as an aryl halide (**3h**) or a Weinreb amide (**3e**). Changing the linker from an O atom to a $CH_2$ resulted in similar reactivity, leading to γ-lactam **3c** instead of a cyclic carbamate. Finally, we show that substitution on the alkene is also well tolerated with the preparation of **3i**, which was obtained as a single diastereoisomer, assigned by NMR as the *syn* product (see SI for details).

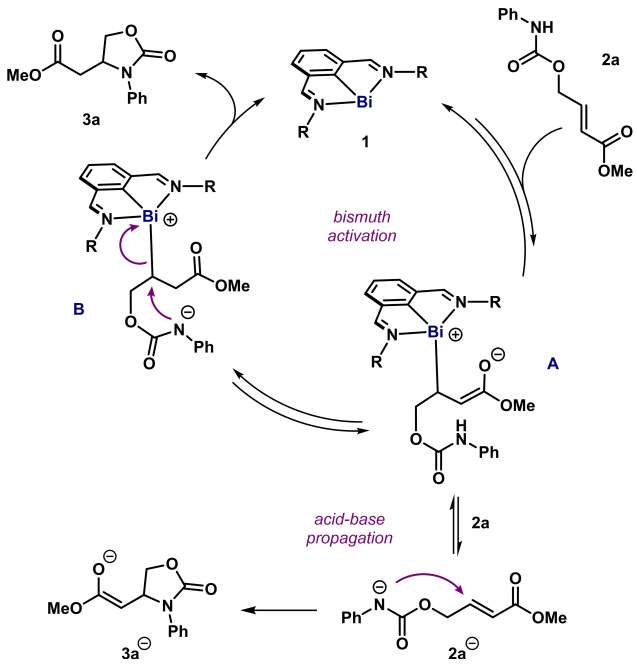
At this point, we conducted a series of experiments to shed light into the putative mechanism. Based on recent findings of low-valent bismuth complexes engaging in a variety of radical-activation processes,[4,15] we evaluated the possibility of a one-electron pathway. First, we conducted our model




**Scheme 2.** Scope of the conjugate aminocyclization. Conversion of **2** was determined by $^1$H NMR analysis of the crude mixture. Isolated yields (0.2–0.5 mmol scale) of **3** are in parenthesis.




**Scheme 3.** Mechanistic investigations. Yields and conversions determined by $^1$H NMR using 1,3,5-trimethoxybenzene as internal standard.




**Scheme 4.** Plausible mechanistic proposal.

reaction in the presence of typical radical scavengers. The reaction of **2a** to give **3a** promoted by **1a** proceeded as usual in the presence of TEMPO, benzoquinone or BHT (Scheme 3A, entries 1–3), suggesting a polar pathway. Moreover, exchanging the α,β-unsaturated carbonyl system for a non-activated alkene led to no cyclization, either in the presence or absence of an external acrylate system (Scheme 3B),[16] suggesting the absence of N-centered radicals.[17] As mentioned before, whereas the reaction does not proceed in the presence of $NEt_3$, less Brønsted-basic but more nucleophilic $PCy_3$ is able to promote the cyclization (Scheme 3C).[18] By analogy to nucleophilic phosphine catalysis, a plausible activation mechanism for **1** is proposed in Scheme 4. Bismuthinidene **1** can be in an equilibrium with bismuth(III) enolate **A** via conjugate addition into the α,β-unsaturated system. It is worth highlighting that $PCy_3$ has extensively been used as nucleophilic catalyst in neutral and redox processes.[19] Moreover, enolates derived from trialkylphosphines have also been characterized and studied as relevant species in the cross-metathesis of acrylates in the presence of second-generation Grubbs catalyst,[20] or proposed as intermediates in Morita-Baylis-Hillman and Rauhut-Currier reactions.[11,12,21] After proton exchange, intermediate **B** would undergo ring-closure giving product **3a** with concomitant regeneration of bismuth(I) **1**. Alternatively, bismuth(III) enolate **A** (a

conceivably stronger base than **1**) could act as a Brønsted base towards another molecule of **2 a**, propagating an acid-base reaction chain initiated by nucleophilic addition. Indeed, whereas $NEt_3$ and AcONa are not active in the reaction (Table 1, entry 9), screening of stronger Brønsted bases showed that 20 mol% of $Cs_2CO_3$ leads to full conversion of **2 a** after 2 h (Scheme 3B, entry 4). This verifies the feasibility of an enolate-mediated propagation, which can be initiated by the redox equilibrium between **1** (or $PCy_3$) and **A** in the presence of **2 a**. It is worth noting that the nucleophilic addition of trialkylphosphines is a known approach for the *in-situ* generation of strong bases.[22]

In conclusion, we found that *N*,*C*,*N*-bismuthinidenes **1** are able to promote a conjugate aminocyclization to afford a variety of cyclic carbamates. Catalyst loadings down to 0.1 mol% of bismuth(I) complex led to excellent yields of the products at room temperature, in short reaction times, and without requiring the addition of an external Brønsted base. Preliminary mechanistic investigations suggest a polar mechanism in which a bismuth(III) enolate could lead to the reaction product either via proton exchange and cyclization upon regeneration of bismuth(I), or via acid-base propagation. This new activation mode for bismuth is supported by the identification of $PCy_3$ as analogous pnictogen nucleophilic catalyst for this transformation.

## Experimental Section

### General Procedure for the Aminocyclization

In an argon-filled glovebox (or in an oven-dried Schlenk flask filled with argon), a glass vial equipped with a Teflon-coated magnetic stirring bar was charged with the corresponding substrate **2** (0.2–0.5 mmol). The substrate was dissolved in anhydrous MeCN (0.2 M; the solvent was purchased from Sigma-Aldrich and stored under 3 Å molecular sieves), and 1 mol% of bismuthinidene **1 a** was added (as a solid when working inside the glovebox, or as a solution in MeCN when using Schlenk techniques). Then, the vial was closed, taken outside the glovebox, and stirred at room temperature for 2 h. After complete conversion of **2** (analyzed by TLC), the solvent was removed in vacuum, and the product was purified by flash column chromatography in silica gel using mixtures of hexanes and ethyl acetate as solvent. For details on experimental procedures, synthesis of starting materials, and full characterization data, see Supporting Information.

## Acknowledgements

*Financial support for this work was provided by the Max-Planck-Gesellschaft and the Max-Planck-Institut für Kohlenforschung. We thank the European Research Council for an ERC Starting Grant to J.C. (ERC StG No. 850496) and the European Union's Horizon Europe research and innovation programme for a Marie Skłodowska-Curie postdoctoral fellowship to M.M. (MSCA-IF Grant No. 101062098). We thank Prof. Dr. A. Fürstner for generous support. We also thank the analytical departments at the MPI-Kohlenforschung. Open Access funding enabled and organized by Projekt DEAL.*

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