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Cyclic Guanidine Organic Catalysts: What Is Magic About Triazabicyclodecene?

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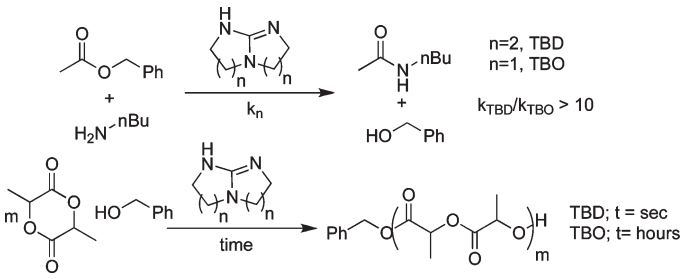

The bicyclic guanidine 1,5,7- triazabicyclo[4.4.0]dec-5-ene (TBD) is an effective organocatalyst for the formation of amides from esters and primary amines. Mechanistic and kinetic investigations support a nucleophilic mechanism where TBD reacts reversibly with esters to generate an acyl-TBD intermediate that acylates amines to generate the amides. Comparative investigations of the analogous bicyclic guanidine 1,4,6-triazabicyclo[3.3.0]oct-4-ene (TBO) reveal it to be a much less active acylation catalyst than TBD. Theoretical and mechanistic studies imply that the higher reactivity of TBD is a consequence of both its higher basicity and nucleophilicity than TBO as well as the high reactivity of the acyl-TBD intermediate, which is sterically prevented from adopting a planar amide structure.

Introduction

Almost a century after its beginnings,[1−4] the field of organocatalysis has undergone a resurgence with the development of new classes of highly enantioselective organocatalysts.[5−8] Notwithstanding the extraordinary pace of developments in transition metal and organometallic catalysis,[9,10] it is clear that organocatalytic reactions have evolved to provide a powerful addition to the armamentarium of methods for chemical synthesis.[5−8] Organocatalysis has also proven a powerful strategy for polymer synthesis.[11] We have investigated a variety of nucleophilic and basic organic molecules as catalysts for transesterification[12,13] and ring-opening polymerization reactions (Figure 1).[11] The highly basic and nucleophilic *N*-heterocyclic carbenes are potent organocatalysts for the ring-opening polymerization of lactones, generating polyesters of defined molecular weights in seconds at room temperature.[11,14] Mechanistic and theoretical studies indicate that *N*-heterocyclic carbenes bind readily

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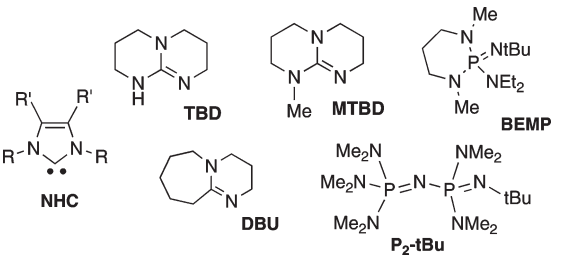

FIGURE 1. Nucleophilic and basic organic catalysts for ring-opening polymerization.

to alcohols,[15,16] activating the alcohol for nucleophilic attack and stabilizing the resulting tetrahedral intermediates.[16,17] In the absence of alcohols, the *N*-heterocyclic carbenes react directly with lactones and mediate the zwitterionic ring-opening polymerization of esters by a nucleophilic mechanism.[14,18] This mechanistic duality is common to many acylation reactions catalyzed by amines and nitrogen heterocycles.[19,20]

In addition to the *N*-heterocyclic carbenes, we have also surveyed a variety of other potent neutral organic bases as catalysts for ring-opening polymerization reactions. Guanidines such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD),[21,22] *N*-methyl-TBD (MTBD), and 1,4,6-triazabicyclo[3.3.0]oct-4-ene (TBO),[21] amidines such as 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU),[23−25] and phosphazenes such as 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) and 1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2Λ^5,4Λ^5- catenadi(phosphazene) (P_2-*t*-Bu)[26] are all effective catalysts for the ring-opening polymerization of lactones and cyclic carbonates[27−32] (Figure 1).

TBD is among the most active ring-opening polymerization catalysts that we have investigated to date. The ring-opening polymerization of lactide with 0.1% TBD in THF exhibits a turnover frequency of 80 s^{-1} at room temperature,[23,25] which is comparable to those of the most active metal catalysts reported for ROP of lactide.[33−35] These polymerizations are also remarkably well-controlled, yielding polylactide with well-defined molecular weights and narrow polydispersities (Figure 2).

TBD is a more active catalyst than MTBD or DBU for lactide polymerization and catalyzes the ring-opening polymerization of δ-valerolactone and ε-caprolactone under conditions where MTBD and DBU are inactive.[23,25] TBD ($TBDH^+$, pK_a = 26), MTBD ($MTBDH^+$, pK_a = 25), and DBU (DBUH+, pK_a = 24) have comparable basicities in THF[36] to those calculated for the *N*-aryl-substituted *N*-heterocyclic carbenes (pK_a 27−28).[37−39] The large differences in activity observed for TBD, MTBD, and DBU imply that thermodynamic basicity is not the sole criterion for predicting catalytic activity.

Guanidines and amidines are effective catalysts for a variety of organic reactions.[22,40−44] These commercially available, easily handled bases have been reported as transesterification catalysts.[27,45−48] In water, guanidines and amidines are readily protonated,[36] and their biological activity[49−51] and much of their reaction chemistry is assumed to proceed via guanidinium or amidinium intermediates.[42−44,51,52] However, several studies have shown that guanidines and amidines can act as nucleophiles.[22,53,54]

We had previously shown that TBD can be acylated by vinyl acetate, implicating that TBD can act as a nucleophile.[23] Subsequent reaction of acyl-TBD with benzyl alcohol

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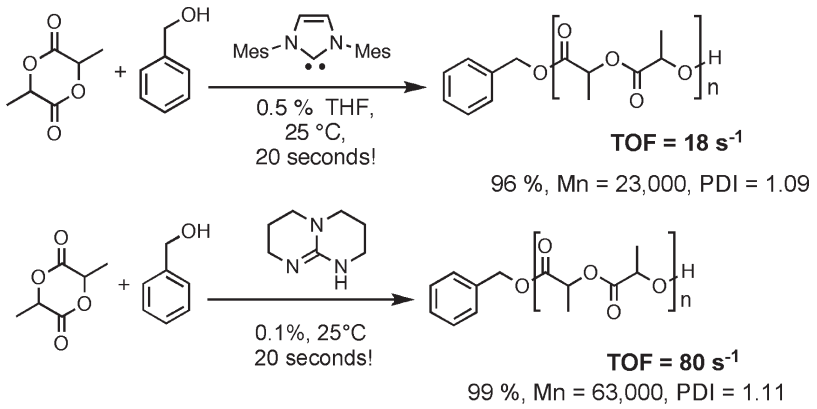

FIGURE 2. Ring-opening polymerization of lactide with TBD is even faster than that with NHC′s.

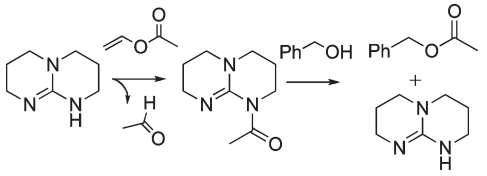

FIGURE 3. Model studies demonstrating the acylating ability of TBD.

yielded the ester, leading us to propose a nucleophilic mechanism as a potential pathway for ring-opening by TBD (Figure 3).[23,25] Subsequent theoretical studies[24,55] indicated that a nucleophilic mechanism was feasible, but had a considerably higher barrier than a hydrogen bond mediated mechanism (Figure 4) for transesterification reactions.

The implication that TBD can act as a bifunctional nucleophilic catalyst suggests that it may be able to acylate other nucleophiles. The acylation of amines is of particular interest as the formation of amides from esters is an exceedingly useful reaction typically carried out under forcing conditions with highly basic catalysts.[56−67] Maggi had previously demonstrated that TBD catalyzes the formation of ureas from carbonates and primary amines,[68,69] and while

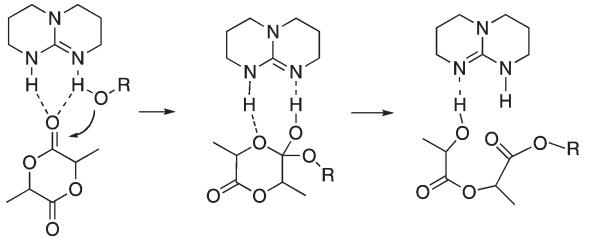

FIGURE 4. Hydrogen-bonding mechanism suggested by theoretical studies.[24,55]

this work was ongoing, Mioskowski reported the aminolyis of esters with amines to form amides under solvent-free conditions.[70]

In this article, we report kinetic studies on the acylation of amines by esters which strongly implicate a nucleophilic mechanism for the conversion of esters to amides in the presence of TBD. Studies of the analogous bicyclic guanidine 1,4,6-triazabicyclo[3.3.0]oct-4-ene (TBO)[21] revealed it to be a much slower catalyst; mechanistic and theoretical studies provide useful insights on the stereoelectronic properties of TBD that contribute to its remarkable ability to catalyze acylation reactions.

Results and Discussion

The amidation of vinyl acetate with 4 equiv of *n*-butylamine with 10 mol % of TBD in toluene solution at 25 °C affords *n*-butylacetamide quantitatively in 6 min (Figure 5). While vinyl esters are known to acylate primary amines in the absence of a catalyst,[71,72] these reactions are significantly slower than that observed in the presence of TBD (6 min vs. 24 h). In the presence of 4 equiv of *n*-butylamine, benzyl acetate converted cleanly (99% conversion, 94.9% isolated yield) to *n*-butylacetamide in 5 h at 80 °C in toluene in the presence of 10 mol % of TBD. Under solvent-free conditions reported by Mioskowski,[70] neat benzyl acetate reacts with 1.3 equiv of butylamine in the presence of 22 mol % of TBD to give *n*-butylacetamide in 89% isolated yield after 2 h.

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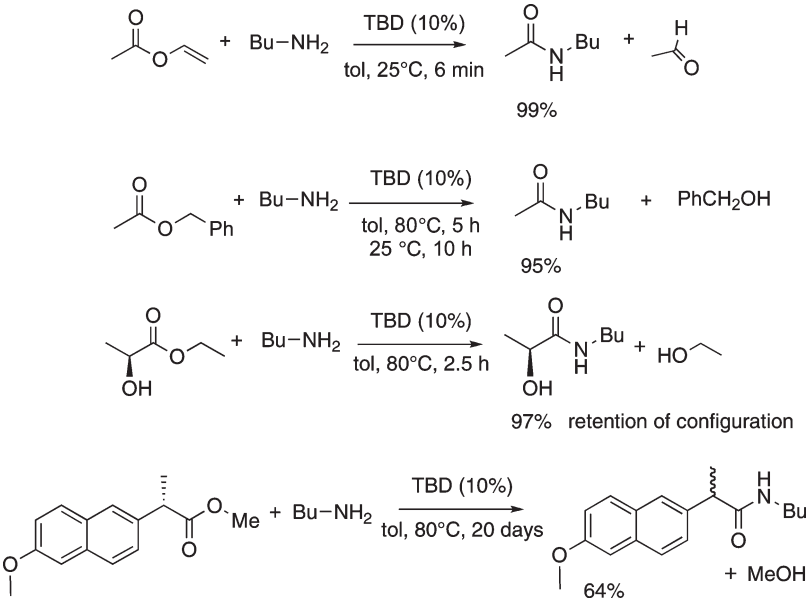

FIGURE 5. Catalytic amidation of esters.

No special care is needed in the purification of solvents: reactions in reagent grade toluene, THF, DMSO, or CH_2Cl_2 proceeded in quantitative yield, albeit with slightly slower rates than those in dry toluene. The conversion of benzyl acetate to *n*-butylacetamide did not proceed at an appreciable rate when *N*-methylTBD (MTBD) or triethylamine was substituted for TBD.

The amidation of (*S*)-ethyl lactate is considerably faster than benzyl acetate, generating a 71% yield of *n*-butyl lactamide within 30 min at 80 °C. Analysis of the Mosher ester of *n*-butyl lactamide reveals it to be of high diastereomeric purity (only one isomer observed by ^{19}F NMR) and derived from (*S*)-*n*-butyl lactamide, indicating that the amidation of ethyl lactate proceeds with retention of configuration with minimal epimerization. In contrast, amidation of the more acidic and sterically demanding (*S*)-2-(6-methoxynaphthalen-2-yl)propionic acid methyl ester was considerably slower (20 days, 64% yield) and yielded racemic *n*-butyl 2-napthyl propranamide. In the latter case, due to the much slower rate, TBD-catalyzed epimerization of either the ester or amide can compete with amidation. Thus, while we had anticipated that the basic nature of TBD might lead to the racemization of acidic esters, it is clear that the extent of racemization depends sensitively on the nature of the ester.

Screening experiments (see the Supporting Information) by ^1H NMR revealed that catalytic formation of amides from branched and secondary amines or from branched esters exhibited much slower rates at 25 °C in solution ($[Ester]_o = 0.23$ M) than those of benzyl acetate and ethyl lactate. However, under solvent-free conditions, the catalytic amidation of methyl phenylacetate yields the amides in 94% yield after 12 h at 75 °C.[70]

Kinetics and Mechanism. Theoretical studies implicate that a hydrogen-bonded mechanism has a lower barrier than a nucleophilic acylation mechanism for transesterification reactions (Figure 4).[24,55] For amine nucleophiles, an H-bonded mechanism analogous to Figure 4 is less likely and motivated us to investigate the chemical and kinetic competence of a nucleophilic mechanism for amine acylation.

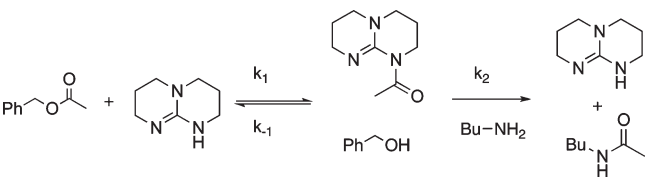

FIGURE 6. Proposed mechanism for formation of *n*-butylacetamide from benzyl acetate and butylamine.

To this end, kinetic investigations of the reaction of benzyl acetate with *n*-butylamine were studied by ^1H NMR in the presence of TBD. In toluene-d_8 at 298 K under pseudo-first-order conditions, the rate of disappearance of benzyl acetate is first order in benzyl acetate, first order in TBD, first order in amine, and inverse first order in benzyl alcohol, yielding a rate law described by eq 1,

$$-\frac{d[\text{Ester}]}{dt} = k_{\text{obs}}\frac{[\text{Ester}][\text{RNH}_2][\text{TBD}]}{[\text{ROH}]} \qquad (1)$$

where [Ester], [RNH_2], [TBD], and [ROH] equal the concentrations of benzyl acetate, *n*-butylamine, TBD, and benzyl alcohol, respectively; and $k_{obs} = 1.9 \pm 0.1 \times 10^{-3}$ M^{-1} s^{-1}. This rate law can be accommodated by the mechanism shown in Figure 6 involving the reversible formation of an acyl-TBD intermediate, followed by irreversible trapping of acyl-TBD with butylamine to generate *n*-butylacetamide and TBD.

Application of the steady-state assumption to the mechanism described in Figure 6 yields the rate law in eq 2:

$$-\frac{d[\text{Ester}]}{dt} = \frac{k_1k_2[\text{Ester}][\text{RNH}_2][\text{TBD}]}{k_{-1}[\text{ROH}] + k_2[\text{RNH}_2]} \qquad (2)$$

This rate equation would be consistent with the experimental rate law under conditions where $k_{-1}[ROH] \gg k_2[RNH_2]$, for which:

$$k_{\text{obs}} = \frac{k_1k_2}{k_{-1}} \qquad (3)$$

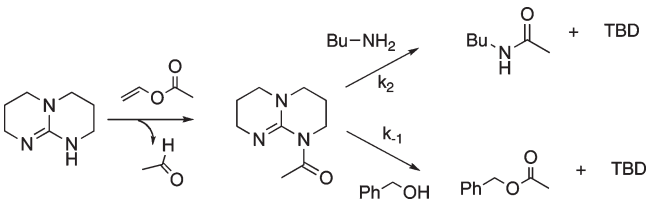

FIGURE 7. Generation of acyl-TBD and acylation with amines and alcohols.

In an effort to demonstrate the validity of this assumption, we measured the individual rate constants for some of the discrete steps of the proposed mechanism in Figure 6. For these studies, acyl-TBD was generated in situ from the reaction of TBD and vinyl acetate (Figure 7).[23] When 10 equiv of butylamine was added to the in situ-generated acyl-TBD intermediate, we observed a first-order decay in acyl-TBD concentration by ^{1}H NMR with a rate constant of $k_2 = 0.9 \pm 0.2 \times 10^{-3}$ M^{-1} s^{-1} (298 K). The reaction of acyl-TBD with excess benzyl alcohol exhibited first-order kinetics and provided an estimate for $k_{-1} = 1.86 \pm 0.39 \times 10^{-2}$ M^{-1} s^{-1} (298 K). The greater than 10-fold difference between these two rate constants supports our approximation used to derive eq 3, and is in accordance with an acyl transfer mechanism defined by a steady-state concentration of acyl-TBD.

Given the kinetic parameters reported above, eq 3 was employed to estimate a value for k_1 equal to $3.7 \pm 0.5 \times 10^{-2}$ M^{-1} s^{-1} under the catalytic conditions used to determine k_{obs}. Independent measurement of k_1 from the reaction of benzyl acetate with TBD was unsuccessful, as a rapid approach to equilibrium did not permit accurate measurement of the forward rate. The equilibrium constant for the formation of the acyl-TBD intermediate in the absence of amine was determined as $K_{eq} = 1.6 \pm 0.2 \times 10^{-4}$ (303 K). Analysis of the temperature dependence of this equilibrium constant yielded the following thermodynamic data: $\Delta H° = 18.22 \pm 0.01$ kJ/mol, $\Delta S° = -1.7 \pm 0.3$ J/mol. These data describe an endergonic reaction between benzyl acetate and TBD, and are consistent with the inverse first-order dependence of the catalytic rate on benzyl alcohol concentration.

Effect of Catalyst Structure. The modest rates for the amidation of sterically demanding substrates with TBD motivated us to investigate less sterically hindered bicyclic guanidines as catalysts. We prepared 1,4,6-triazabicyclo-[3.3.0]oct-4-ene (TBO),[21,73] analogues of which had been shown to be effective catalysts for enantioselective Strecker reactions.[40] We anticipated that the larger N−C−N angle of TBO[22] and the lower basicity of TBO relative to TBD[74] might facilitate reactions with more sterically hindered substrates and potentially mitigate the racemization of α-substituted esters. However, the catalytic activity of TBO for the amidation of benzyl acetate with butylamine was considerably slower than that of TBD. The amidation of benzyl acetate with 10 equiv of butylamine in toluene with 10 mol % of TBO did not proceed at a measurable rate at 25 °C, whereas under comparable conditions TBD catalyzed the amidation of benzyl acetate to butylacetamide in 90% yield after 100 min. At higher temperatures (70 °C), TBO catalyzed the formation of butylacetamide, but in only 20% conversion after 100 min. Kinetic analysis revealed that the observed rate constant for amidation of benzyl acetate by TBO was k_{obs}(TBO, 343 K) $= 2.3 \pm 0.4 \times 10^{-4}$ M^{-1} s^{-1}, whereas that for TBD at 298 K was k_{obs}(TBD, 298 K) $= 1.9 \pm 0.1 \times 10^{-3}$ M^{-1} s^{-1}.

Mechanistic studies were carried out to illuminate the origin of the lower rates observed with TBO relative to TBD. In toluene solution at room temperature, TBD reacts quantitatively with vinyl acetate within minutes to generate acyl-TBD. In contrast the acylation of TBO with vinyl acetate requires over 16 h to generate *N*-acyl-TBO. Isolation of this intermediate provides support for the nucleophilic[75] attack of TBO on vinyl acetate to generate the acylated guanidine, but the slower rate implies that TBO is a less potent nucleophile than TBD. This was supported by experiments with benzyl acetate. Treatment of TBD with 1 equiv of benzyl acetate led to a very rapid reaction to generate an equilibrium mixture of acyl-TBD, benzyl alcohol, and TBD. In contrast, the reaction between TBO and benzyl acetate was much slower, even at elevated temperature. An equimolar mixture of TBO and benzyl acetate (both 0.13 M in toluene) slowly converted to acyl-TBO and benzyl alcohol but even after 100 h at 343 K equilibrium was not established. Likewise, acyl-TBO reacted slowly with benzyl alcohol to generate benzyl acetate but this mixture did not reach equilibrium even after 16 h at 343 K. These data imply that TBO is much less reactive toward esters than TBD, and acyl-TBO is much less reactive toward alcohols than acyl-TBD.

This was confirmed with kinetic studies for the reaction of acyl-TBO with excess butylamine. Under pseudo-first-order conditions, the rate of disappearance of acyl-TBO followed first-order kinetics at 343 K, yielding a rate constant for acylation of butylamine, k_2(ATBO, 343 K) $= 2.6 \pm 0.1 \times 10^{-4}$ M^{-1} s^{-1}. This rate constant is lower than that measured for TBD, k_2(ATBD, 298 K) $= 0.9 \pm 0.2 \times 10^{-3}$ M^{-1} s^{-1}. These data show that the slower rates observed for TBO are a consequence both of the lower nucleophilicity of TBO relative to TBD as well as the slower rate of transacylation of the acylguanidine intermediate.

We turned to computer simulations to elucidate the structural differences between TBD, TBO, and the acylated guanidines, acyl-TBD and acyl-TBO. Coles has previously compared the coordination chemistry of TBD and TBO and has carried out DFT calculations on the geometries and frontier molecular orbitals of these bicyclic guanidines.[76] On the basis of natural bond order analysis (NBO), Coles observed a higher electron density on the imine nitrogen of TBD, relative to that of TBO, consistent with our observations of the higher reactivity of TBD toward vinyl and benzyl acetate.

The structures of acyl-TBD and acyl-TBO were geometry optimized at the B3LYP/6-31G* level with use of Spartan '02 (see the Supporting Information). Analysis of the calculated structures of the two acylated guanidines is revealing. For acyl-TBO, the acyl is coplanar with the guanidine moiety ($C_1-C_2-N_3-C_4$ dihedral angle of 3°), which is consistent

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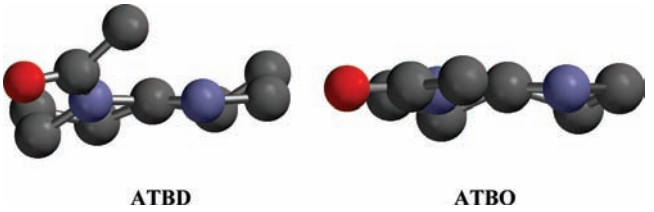


FIGURE 8. B3LYP/6-31G* calculated geometries of ATBD and ATBO.

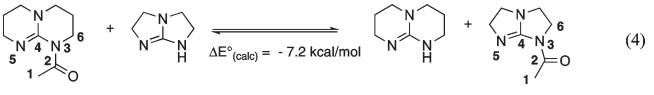
TABLE 1. Polymerization of L-Lactide (L-LA) with TBO[a]

entry	time (hours)	$[M]_0/[I]_0$	conversion[b] (%)	M_n predicted[c]	M_n (GPC)[d]	PDI
1	1.0	100	92	13 200	15 800	1.84
2	2.5	200	82	23 600	18 900	1.90
3	2.5	400	95	54 700	19 500	2.02

[a]Conditions: $[M]_0$ = 1 M, $[TBO]_0$ = 0.04 M in CH_2Cl_2 at room temperature. $[I]_0$ = 11, 5.3, 2.4 mM for entries, 1, 2, and 3, respectively. [b]Monomer conversion as determined by ^1H NMR, using integration of methyl proton resonances of L-LA and the formed polymer. [c]PLA molecular weight predicted based on $([M]_0/[I]_0) \times 144 \times$ conversion. [d]GPC calibrated to polystyrene in THF.

with a planar amide. In contrast, the calculated $C_1-C_2-N_3-C_4$ dihedral angle of acyl-TBD is approximately 15°, indicative of a twisted amide, Figure 8. This deviation from amide planarity is also manifested in the loss of carbonyl-guanidine conjugation (TBD: C_2-N_3 = 1.403 Å; TBO: C_2-N_3 = 1.393 Å) and loss of conjugation within the guanidine moiety (TBD: $(C_4-N)_{max}-(C_4-N)_{min}$ = 0.036 Å; TBO: $(C_4-N)_{max}-(C_4-N)_{min}$ = 0.007 Å). The twisted amide calculated for acyl-TBD might explain its enhanced reactivity toward amine and alcohol nucleophiles. In particular, the much slower rate at which the planar amide of acyl-TBO reacts with amines relative to the twisted amide of acyl-TBD suggests that a planar amide acyl-guanidine intermediate is too stable for effective catalysis.[77]

The same DFT protocol was used to optimize the geometries of TBD and TBO[76] so that an isodesmic acyl-exchange reaction could be calculated, eq 4. The acyl exchange from acyl-TBD to acyl-TBO is predicted to be $\Delta E° = -7.2$ kcal/mol, indicating that the structural differences calculated for acyl-TBD and acyl-TBO are also manifested in a greater thermodynamic stability for acyl-TBO.



(4)

Lactide Polymerization. The relative reactivity of TBD and TBO for amidation of esters is also reflected in their relative reactivity for the ring-opening polymerization (ROP) of lactide (Table 1). The ROP of lactide occurs within minutes in the presence of TBD and an alcohol initiator.[23,25] In contrast, TBO demonstrates much lower catalytic activity. ROP of lactide with 2 mol % of TBO proceeded to 16% conversion after 1 h at room temperature in CH_2Cl_2. To achieve complete conversion over a reasonable time period, catalyst loading was increased to 4 mol %. Under these conditions nearly quantitative monomer conversion was observed after 4 h for various targeted degrees of polymerization (Table 1) but the molecular weight distributions were broad, M_w/M_n = 1.8−2.0. The molecular weights were close to that predicted by the monomer to initiator ratio for target DP = 100 and 200, but were lower than that predicted for DP = 400. Transesterification of the formed polymer chain could account for this lack of control, as the relative rate of polymerization would be reduced due to the lower nucleophilicity of TBO.

Conclusion. The bicyclic guanidine TBD is a potent transacylation catalyst, mediating both the transesterification of esters and the formation of amides from esters. Mechanistic and theoretical studies reveal that TBD can act both as a bifunctional general base/H-bond donor and as a nucleophile for transacylation reactions. For transesterification reactions, a general base mechanism is predicted where H-bonding of the alcohol to TBD simultaneously activates the alcohol toward nucleophilic attack and generates a guanidinium species that stabilizes the tetrahedral intermediate. For amidation reactions, kinetic studies implicate a nucleophilic acylation mechanism where TBD reacts reversibly with the ester to generate a "twisted amide" acyl-TBD intermediate, which subsequently acylates the amine. Comparative investigations of the bicyclic guanidine TBO provide further insights on the unusual geometric features of TBD that render it such an effective acylation catalyst. TBD is both more basic and more nucleophilic than TBO, facilitating the general base/H-bonding transesterification reactions and nucleophilic acylation pathways. In addition, the acyl-guanidine intermediate generated from TBD cannot adopt a planar amide structure, rendering it more active for subsequent acylation by amines.

The unique structural and stereoelectronic features of TBD contribute to its remarkable catalytic activity for transesterification and ring-opening polymerization reactions. More generally, these studies provide further insights on the chemical and biological role of bicyclic guanidine motifs in a number of natural products.[49]

Experimental Section

All syntheses and kinetic studies were performed with standard glovebox and Schlenk techniques, unless stated otherwise. All chemicals were ordered from commercial sources and used as received unless stated otherwise. Toluene-d_8 was distilled from potassium/benzophenone prior to use. Benzyl alcohol was dissolved in THF, stirred overnight over CaH_2, filtered, and recovered by evaporation of the solvent before use. 1,4,6-Triazabicyclo[3.3.0]oct-4-ene (TBO),[21,73] TBO, and *rac*-*N*-butyl-2-hydroxypropanamide[78] were prepared as described in the literature. For kinetic studies of acyl transfer, conversion data were acquired by 300 MHz ^1H NMR, using the integration of the acyl-methyl resonance on benzyl acetate and that of the formed acetamide versus an internal standard (anisole).

Procedure for Kinetic Experiments. To a vial containing 0.8 mL of toluene-d_8 was added 15.0 mg (0.11 mmol) of TBD, 0.1 mL (0.074 g, 1.0 mmol) of *n*-butylamine, and 0.1 mL (0.11 g, 1.0 mmol) of benzyl alcohol. This solution was transferred to an NMR tube, and the reaction was initiated with addition of benzyl actetate (15.4 μL, 16.2 mg, 0.11 mmol). At this point the NMR tube was sealed, removed from the glovebox, and assayed for conversion by ^1H NMR. Disappearance of benzyl acetate and appearance of *n*-butylacetamide were monitored by integration of the benzylic methylene and acyl methyl resonances, respectively. For spectral assignments, see the Supporting Information.

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Typical Substrate Screening Experiment. In a drybox under N_2 atmosphere, TBD (3.2 mg, 0.023 mmol) and *n*-butylamine (67.2 mg, 90.8 μL, 0.92 mmol) were dissolved in 0.5 mL of toluene-d_8 and transferred to an NMR tube. To initiate the reaction, benzyl acetate (34.5 mg, 32.7 μL, 0.23 mmol) was added to the NMR tube by micropipet.

Synthesis of *n*-Butylacetamide (Solution). Into an NMR tube in a drybox was loaded 0.0015 g (0.01 mmol) of TBD, 0.45 mL of toluene-d_8, 0.043 mL (0.44 mmol) of *n*-butylamine, and 0.0155 mL (0.11 mmol) of benzyl acetate. Reaction progress was monitored by ^{1}H NMR. The crude reaction mixture was poured into water and extracted with 3 × 8 mL of diethyl ether and dried with $MgSO_4$, then solvent was removed under reduced pressure, yielding 12 mg (94.9%). Characterization matched the literature.[79]

Synthesis of *n*-Butylacetamide (Neat). Into a vial in a drybox was loaded 67.3 mg (0.48 mmol) of TBD, 0.3237 g (2.17 mmol) of benzyl acetate, and 0.2099 mL (2.88 mmol) of *n*-butylamine. After 2 h, the crude reaction mixture was poured into water and extracted with 3 × 8 mL of diethyl ether and dried with $MgSO_4$, then solvent was removed under reduced pressure, yielding 0.221 g (89%). Characterization matched the literature.[79]

Synthesis of (*S*)-*n*-Butyl-2-hydroxypropanamide. Into an NMR tube in a drybox was loaded 0.0015 g (0.01 mmol) of TBD, 0.7 mL of toluene-d_8, 0.05 mL (0.5 mmol) of *n*-butylamine, and 0.011 mL (0.1 mmol) of ethyl (*S*)-(−)-lactate. Reaction progress was monitored by ^{1}H NMR. The crude reaction mixture was poured into water and extracted with 3 × 8 mL of diethyl ether, organics were dried with $MgSO_4$ and filtered, then solvent was removed under reduced pressure. The residue was shaken with pentane and the solution decanted off the product, yielding 14 mg (97%). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 0.86 (t 3H), 1.16−1.49 (m 7H), 2.21 (s 1H), 3.21 (q 2H), 4.16 (q 1H).[78]

Synthesis of the Mosher Ester. *n*-Butyl-2-hydroxypropanamide (0.003 g, 0.021 mmol, 1 equiv) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.0039 mL, 0.022 mmol, 1.01 equiv) were mixed with carbon tetrachloride (5 drops) and dry pyridine (1 drop) and the mixture was stirred in a closed vial for 20 h. The reaction mixture was extracted with diethyl ether and water and washed twice with ether. After washing with dilute hydrochloric acid and saturated sodium carbonate solution, and drying with $MgSO_4$, the mixture was filtered and solvent was evaporated under reduced pressure. NMR spectra were taken without further purification.

Synthesis of (*S*)-Naproxen Methyl Ester. In a three-necked round-bottomed flask equipped with a reflux condenser, 0.94 g (4.09 mmol) of (*S*)-naproxen was stirred in 20 mL of methanol under N_2. The flask was cooled to 0 °C and 0.049 mL (0.68 mmol) of thionyl chloride was added dropwise via syringe. The mixture was warmed to room temperature over an hour and refluxed for 6 h. Volatiles were removed under high vacuum Yield 0.60 g, 60.5%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 1.51 (d 3H), 3.59 (s 3H), 3.79 (q 1H), 3.84 (s 3H), 7.02−7.66 (m 6H); $[\alpha]^{24.5}_D$ +79.65 (*c* 26 mg/100 mL; CH_2Cl_2), $[\alpha]_{D,Lit}$ +76.9 (*c* 20 mg/ 100 mL; $CDCl_3$).[80]

Synthesis of *rac*-Naproxen Methyl Ester. Racemic naproxen methyl ester was made by dissolving 0.2 g (0.819 mmol) of (*S*)-naproxen methyl ester in 10 mL of methanol with 0.02 g (0.164 mmol) of 5-diazabicyclo[4.3.0]non-5-ene and refluxing overnight. The methanol solution was diluted with 50 mL of water and extracted with 3 × 25 mL of methylene chloride and dried over $MgSO_4$, then solvent was removed under reduced pressure, yielding 0.196 mg (97.9%). $[\alpha]^{23.7}_D$ +0.0018 (*c* 26 mg/ 1 mL; CH_2Cl_2).

Synthesis of (*S*)-Naproxen Butyl Amide.[81]**.** In a drybox, an NMR tube was loaded with 1.6 mg (0.012 mmol) of TBD, 1 mL of toluene-d_8, 0.046 mL (0.46 mmol) of *n*-butylamine, and 28 mg (0.115 mmol) of (*S*)-naproxen methyl ester. Reaction conversion was monitored by ^{1}H NMR. After several days, the reaction had reached 65% conversion and was quenched by being poured into water. The water was extracted with 3 × 8 mL of diethyl ether, organics were dried with $MgSO_4$, then solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with use of ethyl acetate: hexanes (1:2). Yield: 21 mg (0.073 mmol, 63.7%). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 0.77 (t 3H), 1.06−1.37 (m 4H), 1.53 (d 2H), 3.11 (q 2H), 3.61 (q 1H), 3.86 (s 3H), 5.23 (s 1H), 7.05−7.69 (m 6H). $[\alpha]^{24.5}_D$ +1.11 (*c* 20.9 mg/1 mL; CH_2Cl_2). HPLC: 99:10 heptane/2-propanol; flow rate = 0.8 mL/min; t_1 = 12.3 min, t_2 = 14.4 min.

Synthesis of 1,4,6-Triazabicyclo[3.3.0]oct-4-ene (TBO). TBO was synthesized by the method of Cotton, et al.[73] With stirring at room temperature under nitrogen atmosphere, xylenes (300 mL), diethylenetriamine (20.6 g, 21.7 mL, 0.2 mol), and carbon disulfide (15.2 g, 12.0 mL, 0.2 mol) were added to a three-necked flask. A white precipitate formed immediately and the suspension was heated to reflux. Evolution of H_2S from the reaction exhaust was monitored by using filter paper soaked in a methanolic suspension of lead(II) acetate. After 10 days of reflux under nitrogen, GC/MS analysis confirmed quantitative conversion to the target compound. Upon cooling to room temperature a white solid crystallized from solution, and the supernatant was decanted. The solid was washed with 2 × 50 mL portions of acetone and pentane, respectively, and dried under vacuum overnight (8.65 g, 39%). ^{1}H NMR 400 MHz ($CDCl_3$) δ 6.02 (br s, 1H), 3.79 (t, 2H, J = 7.0 Hz), 3.05 (t, 2H, J = 7.0 Hz). ^{13}C NMR 100 MHz ($CDCl_3$) δ 171.2, 52.6, 49.4. LRMS (*m*/*z*): 112.1 (positive ion, M + H).

Synthesis of 1-(2,3,5,6-Tetrahydro-1*H*-imidazo[1,2-*a*]imidazol-1-yl)ethanone (acyl-TBO). With stirring at room temperature in a drybox, THF (5 mL), TBO (0.115 g, 1.03 mmol), and vinyl acetate (0.1 mL, 0.09 g, 1.1 mmol) were added to a 20 mL glass vial. The solution was stirred for approximately 16 h, at which point solvent and all volatiles were removed under vacuum, yielding a slightly off-white solid (0.143 g, 0.93 mmol, 90.3%). ^{1}H NMR 400 MHz (toluene-d_8) δ 3.77 (t, 2H, J = 7.8 Hz), 3.62 (t, 2H, J = 7.0 Hz), 2.51 (s, 3H), 2.45 (t, 2H, J = 7.2 Hz), 2.14 (t, 2H, J = 7.0 Hz). ^{13}C NMR 100 MHz (toluene-d_8) δ 168.5, 59.6, 50.8, 48.4, 44.3, 23.1. LRMS (*m*/*z*): 154.2 (positive ion, M + H). Elemental Anal. Calcd: C, 54.89; H, 7.24; N, 27.43. Found: C, 54.71; H, 7.23; N, 27.20.

Polymerization of L-LA with TBO Catalyst. L-LA (300 mg, 2.1 mmol) and TBO (10.0 mg, 0.1 mmol) were dissolved in CH_2Cl_2 (2 mL). To initiate the polymerization benzyl alcohol (2.2 μL, 0.02 mmol) was added. The polymerization was quenched after 1 h by addition of excess benzoic acid (~20 mg, 0.16 mmol), and solvent was removed under vacuum. ^{1}H NMR ($CDCl_3$) δ 8.15−7.45 (5H), 5.30−5.13 (m, ~200H), 4.4 (t, 2H), 1.67−1.43 (br d). GPC (RI detection, polystyrene calibration): M_n = 15 800 g mol^{-1}, PDI = 1.84.

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Supporting Information Available: Relevant NMR data, kinetics and thermodynamic data, substrate sceening, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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