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Enantioselective N-Heterocyclic Carbene-Catalyzed Synthesis of Trifluoromethyldihydropyridinones

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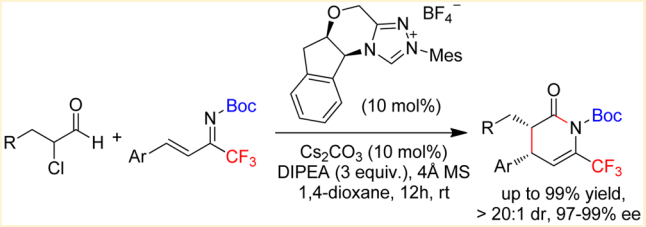
Supporting Information

ABSTRACT: The enantioselective N-heterocyclic carbene-catalyzed [4 + 2] cyclocondensation of α-chloroaldehydes and trifluoromethyl *N*-Boc azadienes was developed, giving the corresponding 3,4-disubstituted-6-trifluoromethyldihydropyridin-2(1*H*)-ones in good yields with exclusive *cis*-selectivities and excellent enantioselectivities.



Incorporation of fluorine into molecules can bring notable changes in physical and chemical properties.[1] Among them, trifluoromethyl group is one of the most important fluorine-containing functional groups for its addition of metabolic stability and lipophilicity.[2] On the other hand, dihydropyridinones are widely present in various bioactive compounds.[3] Combined with these two features, trifluoromethyldihydropyridinone would be an interesting target for organic synthesis.[4]

In the past decades, N-heterocyclic carbenes (NHCs) have been demonstrated as efficient organocatalysts for a wide variety of reactions of aldehydes,[5] epoxy aldehydes,[6] α-haloaldehdyes,[7] enals,[8] ketenes,[9] esters,[10] Michael acceptors,[11] and others.[12] The hetero-Diels−Alder (HDA) reactions of 1-azadienes are powerful approaches to the synthesis of six-membered N-heterocycles.[13] The NHC-catalyzed cyclization reactions with azadienes for the synthesis of N-heterocycles have also been reported, including the reaction of enals with azadienes by Bode et al.[14] and the reaction of esters with azadienes by Chi et al.[15] The NHC-catalyzed [4 + 2] cyclization reaction of ketenes and chloroaldehydes with azadienes was developed in our group.[16] Considering the importance of trifluoromethylated compounds, we are interested in the NHC-catalyzed synthesis of trifluoromethylated heterocycles.[17] In this paper, we report the enantioselective synthesis of trifluoromethylated dihydropyridinones.[18]

Initially, the reaction of α-chloroaldehyde **1a** and trifluoromethyl azadiene **2a** was investigated under NHC catalysis (Table 1). Although the NHC-catalzyed reaction of ketene or α-chloraldehyde with trifluoromethyl azadiene gave no or only a trace of the desired cycloadduct, we were encouraged to find that the reaction of chloroaldehyde **1a** catalyzed by tetracyclic NHC **A1**′[19] gave the desired trifluoromethyl dihydropyridinone **3a** in 26% yield with 92% ee (entry 1). Various bases were then screened for the reaction (entries 1−5). It is interesting that DIPEA afforded the best enantioselectivity, while Cs_2CO_3 was the best choice for yield. Considering the two roles of the base(s) to deprotonate the NHC precursor and remove the hydrochloride, mixed bases were then investigated. We were happy to find that both the yield and enantioselectivity were improved when the mixed bases of Cs_2CO_3 (0.1 equiv) and DIPEA (3.0 equiv) were employed for the reaction (entry 6). NHC precursor **A2** and **A3** with different N-substituents resulted in low yields (entries 7 and 8). Both the reactions using NHC precursor **B** derived from L-pyroglutamic acid and the NHC precursor **C** with a free hydroxyl group gave only trace of the desired cycloadduct (entries 9 and 10). Optimization of solvents showed that 1,4-dioxane was the best (entries 11 and 12). Further improvements were realized when 4 Å molecular sieves (4 Å MS) was added, giving the desired trifluoromethyl dihydropyridinone **3a** in 86% yield with 99% ee (entry 13). Reducing the loading of NHC precursor to 5 mol % resulted in some loss of the yield but without erosion of the enantioselectivity (entry 14).

With the optimized condition in hand, a variety of azadienes was investigated for the reaction (Table 2). Both azadienes with electron-donating groups (Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$) and with electron-withdrawing groups (Ar = 4-ClC_6H_4, 4-BrC_6H_4) worked well, giving the desired dihydropyridinones (**3b−3d**) in good yields with exclusive cis-selectivities and excellent enantioselectivities. Substituents at the *meta*-position (Ar = 3-MeC_6H_4, 3-ClC_6H_4) and *ortho*-position (Ar = 2-MeC_6H_4, 2-ClC_6H_4) were also well tolerated, giving the dihydropyridinones (**3f−3i**) in slightly decreased yields with high enantioselectivities. The azadiene with 2-furyl group afforded cycloadduct **3j** in 78% yield with 99% ee. Notably, α-chloroaldehydes with varied linear aliphatic chains reacted well, giving the desired cycloadducts (**3k−3p**) in good to high yields with exclusive diastereo- and excellent enantioselectiv-

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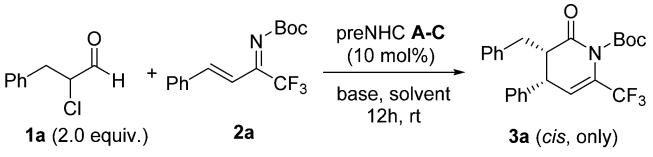
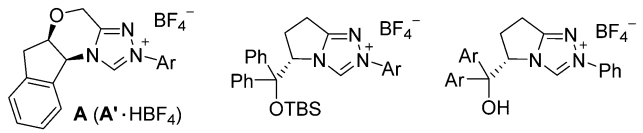
Table 1. Optimization of Reaction Conditions





A1 Ar = Mes
A2 Ar = Ph
A3 Ar = 2-*i*-PrC$_6$H$_4$

Ar = 2-*i*-PrC$_6$H$_4$
B (**B'**·HBF$_4$)

Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
C (**C'**·HBF$_4$)'

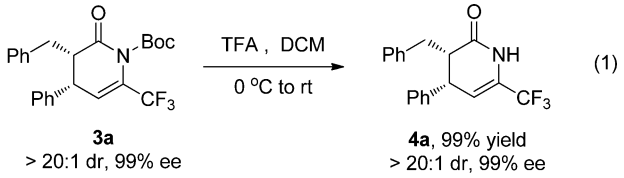
entry	cat	base[a]	solvent	yield (%)[b]	ee (%)[c]
1	**A1**	DIPEA	DCM	26	92
2	**A1**	K_2CO_3	DCM	36	90
3	**A1**	Cs_2CO_3	DCM	40	89
4	**A1**	Et_3N	DCM	13	87
5	**A1**	DMAP	DCM	20	90
6	**A1**	Cs_2CO_3, DIPEA	DCM	61	99
7	**A2**	Cs_2CO_3, DPIEA	DCM	19	99
8	**A3**	Cs_2CO_3, DIPEA	DCM	19	99
9	**B**	Cs_2CO_3, DIPEA	DCM	trace	ND
10	**C**	Cs_2CO_3, DIPEA	DCM	trace	ND
11	**A1**	Cs_2CO_3, DIPEA	THF	65	98
12	**A1**	Cs_2CO_3, DIPEA	1,4-dioxane	77	99
13[d]	**A1**	Cs_2CO_3, DIPEA	1,4-dioxane	86	99
14[f]	**A1**	Cs_2CO_3, DIPEA	1,4-dioxane	71	99

[a]One base (3.0 equiv) for entries 1−5, or mixed bases of Cs_2CO_3 (0.1 equiv) and DIPEA (3.0 equiv) for entries 6−14. [b]Isolated yield. [c]Determined by chiral HPLC. [d]4 Å MS (50 mg) was added. [f]NHC precursor (5 mol %) was employed.

ities. In addition, α-chloroaldehyde with branched aliphatic chain could give the corresponding annulation product in excellent enantioselectivity albeit in low yield (**3q**).

The absolute configuration of cycloadduct **3e** was determined by the X-ray analysis of its crystal (Figure S1).

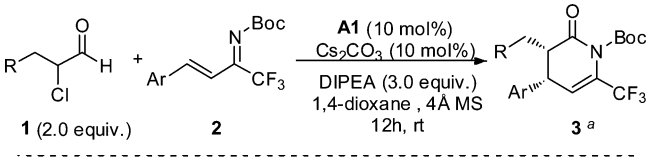
Although the inverse-electron-demanded DA reactions with *N*-tosyl azadienes have been well established in literatures, the corresponding reaction with *N*-Boc azadienes remains unexplored. In our work, the *N*-Boc azadienes **2** were successfully employed, as expected, and the protective Boc group could be easily removed by TFA in DCM, giving the corresponding dihydropyridinone **4a** in 99% yield without the erosion of enantioselectivity (eq 1).

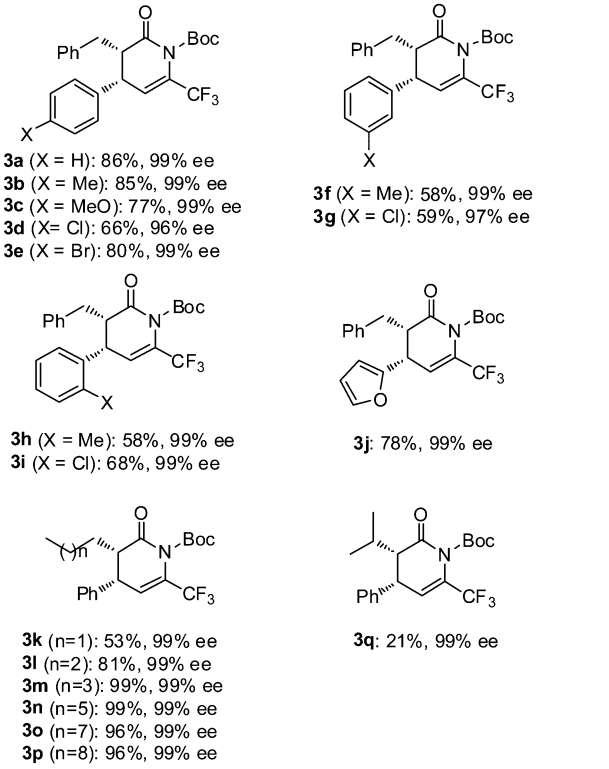


(1)

A plausible catalytic cycle for the reaction is depicted in Figure 1. The addition of NHC catalyst to chloroaldehyde **1** gives the zwitterionic intermediate **I**,[20] which is converted to the corresponding enolate **II** by elimination of hydrogen chloride in the presence of base. The [4 + 2] cycloaddition of enolate **II** and trifluoromethyl azadiene **2** affords the cycloadduct **III**. The fragmentation of cycloadduct **III** affords the

Table 2. Reaction Scope





3a (X = H): 86%, 99% ee
3b (X = Me): 85%, 99% ee
3c (X = MeO): 77%, 99% ee
3d (X= Cl): 66%, 96% ee
3e (X = Br): 80%, 99% ee

3f (X = Me): 58%, 99% ee
3g (X = Cl): 59%, 97% ee

3h (X = Me): 58%, 99% ee
3i (X = Cl): 68%, 99% ee

3j: 78%, 99% ee

3k (n=1): 53%, 99% ee
3l (n=2): 81%, 99% ee
3m (n=3): 99%, 99% ee
3n (n=5): 99%, 99% ee
3o (n=7): 96%, 99% ee
3p (n=8): 96%, 99% ee

3q: 21%, 99% ee

[a]Isolated yield with dr > 20:1 for all cases.

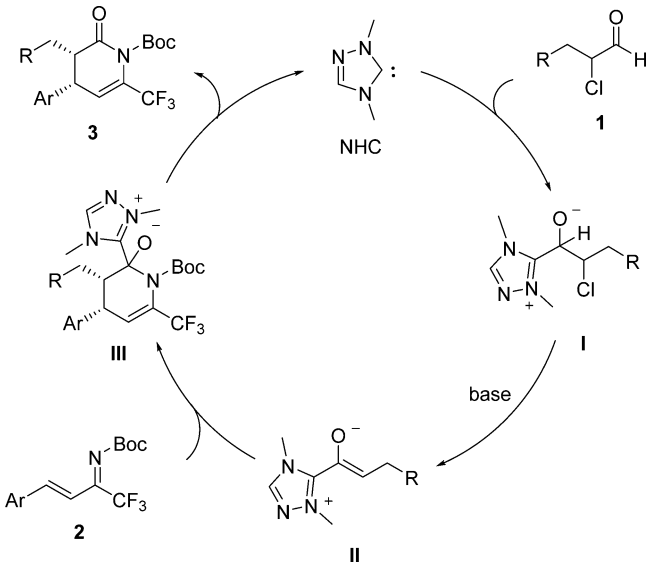


Figure 1. Plausible catalytic cycle.

final dihydropyridinone **3** and regenerates the NHC catalyst. It should be noted that an alternative pathway via stepwise Michael addition of enolate **II** to azadiene followed by intramolecular amidation is also possible. However, the exclusive cis-selectivities observed make us believe that the

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concerted [4 + 2] cycloaddition is favored over the stepwise pathway.

The possible stereocontrol mode via endo-selectivity Diels–Alder reaction is depicted in Figure 2. When the R group in enals is an aryl group, the π-stacking of the two aryl groups in enal and azadiene favors the endo-selectivity.

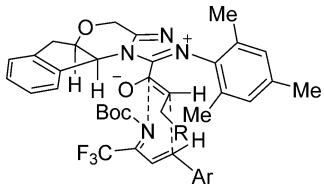


Figure 2. Possible stereochemical mode.

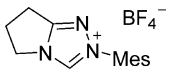
In summary, the enantioselective N-heterocyclic carbene-catalyzed [4 + 2] cyclocondensation of α-chloroaldehydes and trifluoromethyl *N*-Boc azadienes was developed. The reaction worked well for both aryl and aliphatic α-chloroaldehydes, giving the corresponding 3,4-disubstituted-6-trifluoromethyl dihydropyrindinones in good yields with exclusive cis-selectivities and excellent enantioselectivities.

EXPERIMENTAL SECTION

General Methods. Unless otherwise indicated, all reactions were carried out under nitrogen atmosphere in oven-dried glassware with magnetic stirring. All solvents were dried and distilled by standard procedures. NHC precursors, chloroaldehydes, and trifluoromethyl substituted α,β-unsaturated imines were prepared according to literatures.[21] Column chromatograph was performed on silica gel 200–300 mesh.

Typical Procedure. To an oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with precatalyst **A1** (14.0 mg, 0.03 mmol) and anhydrous Cs_2CO_3 (9.7 mg, 0.03 mmol). This tube was closed with a septum, evacuated, and backfilled with argon. To this mixture was added freshly distilled 1,4-dioxane (2 mL) while stirring for several minutes at room temperature, then DIPEA (218 μL, 0.6 mmol), chloroaldehyde **1a** (109.64 mg, 0.6 mmol), and trifluoromethyl azadiene **2a** (89.8 mg, 0.3 mmol) were added. After stirring for 24 h, the reaction mixture was diluted with diethyl ether and passed through a short silica pad. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether, typically 1/100) to give the desired cycloadduct **3**.

Racemic samples for the chiral phase HPLC analysis were prepared using triazolium **D** as the NHC precatalyst under the same conditions.



D

*(3S,4S)-tert-Butyl3-benzyl-2-oxo-4-phenyl-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3a**).* Colorless oil, 111.2 mg, 86%. R_f = 0.5 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +175.0 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 10.3 min (major), 12.5 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.20 (m, 7H), 7.12–7.10 (m, 4H), 6.27 (d, *J* = 7.2 Hz, 1H), 3.60 (t, *J* = 6.3 Hz, 1H), 3.27–3.20 (m, 2H), 2.37–2.30 (m, 1H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 149.9, 138.7, 135.3, 130.2, 130.1, 129.9 (q, *J* = 35.1 Hz), 129.5, 129.2, 129.1, 128.7, 128.7, 128.3, 126.7, 121.8, 119.4 (q, *J* = 4.2 Hz), 119.3, 119.1, 86.0, 47.2, 40.5, 31.7, 29.8, 27.5. ^{19}F NMR (471 MHz, $CDCl_3$) δ −63.24 (s). IR (KBr): 3566, 3030, 2982, 2933, 1783, 1715, 1144, 698. HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{24}H_{24}F_3NO_3Na^+$, 454.15921; found, 454.16005.

*(3S,4S)-tert-Butyl3-benzyl-2-oxo-4-(p-tolyl)-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3b**).* Colorless oil, 115.6 mg, 85%. R_f = 0.4 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +172.7 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 9.7 min (major), 11.1 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, *J* = 7.3 Hz, 2H), 7.18–7.15 (m, 1H), 7.05 (t, *J* = 7.3 Hz, 4H), 7.93 (d, *J* = 8.1 Hz, 2H), 6.18 (d, *J* = 7.3 Hz, 1H), 3.49 (t, *J* = 6.2 Hz, 1H), 3.19–3.11 (m, 2H), 2.30–2.23 (m, 4H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 149.8, 138.7, 138.0, 132.0, 130.3, 129.9, 129.8, 129.6, 129.0, 128.6 (q, *J* = 35.0 Hz), 128.4, 126.5, 119.5 (q, *J* = 4.1 Hz), 119.0, 85.8, 47.2, 40.0, 31.5, 27.4, 21.1. IR (KBr): 3566, 3029, 2982, 1783, 1716, 1146, 699. HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd. for $C_{25}H_{26}F_3NO_3Na^+$, 468.17493; found, 488.17570.

*(3S,4S)-tert-butyl3-benzyl-4-(4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3c**).* Colorless oil, 110.0 mg, 77%. R_f = 0.3 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +193.6 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 11.2 min (major), 14.4 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.28 (m, 2H), 7.24–7.21 (m, 1H), 7.13–7.11 (m, 2H), 7.04–7.01 (m, 2H), 6.87–6.84 (m, 2H), 6.25 (d, *J* = 7.3 Hz, 1H), 3.81 (s, 3H), 3.54 (t, *J* = 6.4 Hz, 1H), 3.27–3.17 (m, 2H), 2.37–2.31 (m, 1H), 1.58 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 159.5, 150.0, 138.7, 129.8, 129.7, 129.5, 129.2 (d, *J* = 34.9 Hz), 129.0, 128.8, 128.7, 128.6, 127.4, 127.3, 126.9, 126.5, 121.7, 119.6 (d, *J* = 4.1 Hz), 119.0, 114.5, 85.8, 55.3, 47.2, 39.6, 31.6, 27.4. IR (KBr): 3545, 2929, 2856, 1784, 1716, 1147, 699. HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{25}H_{26}F_3NO_4Na^+$, 484.17007; found, 484.17061.

*(3S,4S)-tert-Butyl3-benzyl-4-(4-chlorophenyl)-2-oxo-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3d**).* Colorless oil, 92.5 mg, 66%. R_f = 0.5 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +131.5 (*c* 1.0, $CHCl_3$), HPLC analysis: 96% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 11.2 min (major), 12.3 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.16(m, 5H), 7.05–7.01 (m, 3H), 6.91 (dt, *J* = 7.0, 1.5 Hz, 1H), 6.17 (d, *J* = 7.4 Hz, 1H), 3.52–3.48 (m, 1H), 3.17 (dd, *J* = 12.5, 7.8 Hz, 2H), 2.28–2.21 (m, 1H), 1.53 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 149.4, 138.3, 137.2, 135.0, 130.4 (q, *J* = 35.2 Hz), 129.0, 128.8, 128.7, 128.6, 126.9, 126.8, 118.8, 118.7 (q, *J* = 4.1 Hz), 86.4, 47.0, 40.0, 31.7, 27.5. IR (KBr): 3566, 2961, 2935, 1784, 1716, 1146, 699. HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{24}H_{23}ClF_3NO_3Na^+$, 488.12039; found, 488.12108.

*(3S,4S)-tert-**b**utyl3-benzyl-4-(4-bromophenyl)-2-oxo-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3e**).* Colorless oil, 122.5 mg, 80%. R_f = 0.4 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +200.0 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 10.1 min (major), 11.6 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.29–7.24 (m, 1H), 7.11 (d, *J* = 7.4 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.24 (d, *J* = 7.3 Hz, 1H), 3.56 (t, *J* = 6.5 Hz, 1H), 3.29–3.21 (m, 2H), 2.34–2.26(m, 1H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 149.7, 138.2, 134.2, 132.2, 130.5, 130.2, 130.1, 130.0, 128.9, 128.7 (q, *J* = 34,9 Hz),, 128.5, 126.7, 122.3, 121.6, 118.8, 118.6 (q, *J* = 4.2 Hz)., 86.1, 46.7, 39.7, 31.5, 27.4. ^{19}F NMR (471 MHz, $CDCl_3$): δ −63.38 (s). IR (KBr): 3566, 3029, 2982, 1783, 1716, 1144, 699. HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{24}H_{23}BrF_3NO_3Na^+$, 532.06958; found, 532.07056.

*(3S,4S)-tert-Butyl3-benzyl-2-oxo-4-(m-tolyl)-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3f**).* Colorless oil, 78.8 mg, 58%. R_f = 0.5 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +158.2 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 9.3 min (major), 10.3 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, *J* = 7.3 Hz, 2H), 7.17–7.11 (m, 2H), 7.03 (d, *J* = 7.2 Hz, 3H), 6.80 (d, *J* = 6.0 Hz, 2H), 6.18 (d, *J* = 7.3 Hz, 1H), 3.37 (dd, *J* = 17.9, 11.8 Hz, 1H), 3.18–3.01 (m, 2H), 2.27–2.23 (m, 4H), 1.52 (d, *J* = 6.6 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 149.9, 138.8, 138.8, 135.2, 130.2, 129.9 (q, *J* = 35.0 Hz), 129.5, 129.2, 129.1, 129.0, 128.7, 126.7, 125.8, 121.8, 119.6 (q, *J* = 4.1 Hz), 119.1, 40.5, 31.7, 27.5, 21.6.

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IR (KBr): 3566, 3218, 2960, 1688, 1507, 1298, 698. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{25}H_{26}F_3NO_3Na^+$, 468.17508; found, 468.17570.

*(3S,4S)-tert-Butyl3-benzyl-4-(3-chlorophenyl)-2-oxo-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3g**).* Colorless oil, 82.2 mg, 59%. R_f = 0.5 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +257.7 (*c* 1.0, $CHCl_3$), HPLC analysis: 97% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 11.6 min (major), 12.9 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.15 (m, 5H), 7.06−7.01 (m, 3H), 6.92 (dd, *J* = 4.2, 2.8 Hz, 1H), 6.18 (d, *J* = 7.4 Hz, 1H), 3.50 (t, *J* = 6.2 Hz, 1H), 3.22−3.14 (m, 2H), 2.28−2.21 (m, 1H), 1.53 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 149.3, 138.2, 137.1, 135.0, 130.8, 130.5, 130.3, 129.0, 128.7 (q, *J* = 35.1 Hz), 128.5, 126.8, 126.7, 121.6, 118.9, 118.7, 118.6 (q, *J* = 4.3 Hz), 86.3, 46.8, 39.9, 31.6, 27.4. IR (KBr): 3566, 3029, 2984, 1785, 1716, 1145, 698. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{24}H_{23}ClF_3NO_3Na^+$, 488.12009; found, 488.12108.

*(3S,4S)-tert-Butyl3-benzyl-2-oxo-4-(o-tolyl)-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3h**).* Colorless oil, 78.8 mg, 58%. R_f = 0.5 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +166.0 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 9.9 min (major), 13.2 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18−7.08 (m, 8H), 6.84−6.82(m, 2H), 6.09 (d, *J* = 6.9 Hz, 1H), 3.78 (t, *J* = 6.8 Hz, 1H), 3.26−3.21 (m, 1H), 3.16−3.10 (m, 1H), 2.44−2.38 (m, 1H), 1.91 (s, 3H), 1.50 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 149.8, 138.4, 136.2, 134.9, 131.1, 129.1, 128.9 (q, *J* = 35.1 Hz), 128.8, 128.7, 128.6, 127.9, 127.3, 127.0, 126.7, 121.7, 119.0, 117.9 (q, *J* = 4.3 Hz), 117.7, 85.9, 74.5, 58.4, 45.9, 35.6, 31.8, 27.5, 19.6. IR (KBr): 3566, 3029, 2981, 1780, 1715, 1144, 699. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{25}H_{26}F_3NO_3Na^+$, 468.17490; found, 468.17570.

*(3S,4S)-tert-Butyl3-benzyl-4-(2-chlorophenyl)-2-oxo-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3i**).* Colorless oil, 95.0 mg, 68%. R_f = 0.5 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +144.8 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 9.3 min (major), 15.3 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dt, *J* = 8.1, 1.6 Hz, 1H), 7.23−7.11 (m, 6H), 6.92−6.90 (m, 2H), 6.18 (d, *J* = 6.9 Hz, 1H), 4.24 (td, *J* = 6.8, 1.6 Hz, 1H), 3.13 (dd, *J* = 14.1, 9.1 Hz, 2H), 2.52−2.45 (m, 1H), 1.49 (s, 9H) ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 149.6, 138.4, 134.1, 130.2, 129.8, 129.5 (q, *J* = 35.0 Hz), 129.2, 128.9, 128.6, 128.4, 127.9, 126.6, 121.5, 118.8, 117.3 (q, *J* = 4.3 Hz), 85.9, 46.2, 36.3,, 31.7, 27.3. IR (KBr): 3566, 3030, 2982, 1780, 1715, 1145, 699. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{24}H_{23}ClF_3NO_3Na^+$, 488.12039; found, 488.12108.

*(3S,4S)-tert-Butyl3-benzyl-4-(furan-2-yl)-2-oxo-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3j**).* Colorless oil, 98.6 mg, 78%. R_f = 0.5 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +139.9 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 10.7 min (major), 14.8 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, 2.6 Hz, 1H), 7.25−7.22 (m, 2H), 7.17−7.12 (m, 3H), 6.27 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.13 (dd, *J* = 9.7, 5.4 Hz, 2H), 3.59 (t, *J* = 6.4 Hz, 1H), 3.29−3.24 (m, 1H), 2.96−2.90 (m, 1H), 2.35 (dd, *J* = 14.4, 10.3 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 149.4, 148.9, 143.0, 138.6, 131.7, 131.13 (q, *J* = 35.3 Hz), 129.2, 128.6, 126.6, 121.6, 118.9, 117.4 (q, *J* = 4.1 Hz), 110.6, 108.7,85.6, 47.6, 33.2, 32.0, 27.4. IR (KBr): 3545, 2929, 2856, 1784, 1716, 1147, 699. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{22}H_{22}F_3NO_4Na^+$, 444.13898; found, 444.13931.

*(3S,4S)-tert-Butyl2-oxo-4-phenyl-3-propyl-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3k**).* Colorless oil, 61.9 mg, 53%. R_f = 0.7 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +113.0 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 8.8 min (major), 11.8 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.25 (m, 3H), 7.18−7.16 (m, 2H), 6.32 (d, *J* = 6.3 Hz, 1H), 3.77 (dd, *J* = 6.6, 5.4 Hz, 1H), 2.78 (q, *J* = 6.8 Hz, 1H), 1.62−1.58 (m, 10H), 1.44−1.37 (m, 2H), 1.37−1.11 (m, 1H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 150.1, 135.6, 130.2 (q, *J* = 34.9 Hz), 129.1, 128.3, 128.1, 121.9, 119.3, 119.2, 119.1 (q, *J* = 4.1 Hz), 85.8, 45.8, 41.5, 28.2, 27.5, 20.7, 14.1. IR (KBr): 3566, 2961, 2935, 1784, 1716, 1146, 699. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{24}F_3NO_3Na^+$, 406.15947; found, 406.16005.

*(3S,4S)-tert-Butyl3-butyl-2-oxo-4-phenyl-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3l**).* Colorless oil, 97.0 mg, 81%. $[\alpha]_D^{20}$ +250.0 (**c** 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 8.7 min (major), 11.6 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.17 (m, 3H), 7.11−7.08 (m, 2H), 6.24 (d, *J* = 6.9 Hz, 1H), 3.71−3.68 (m, 1H), 2.67 (t, *J* = 6.8 Hz, 1H), 1.55−1.54 (m, 1H), 1.50 (s, 9H), 1.32−1.26 (m, 4H), 1.22−1.17 (m, 1H), 0.77 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 150.1, 135.6, 130.9, 130.5, 130.2 (q, *J* = 35.0 Hz), 129.8, 129.1, 128.3, 128.1, 124.6, 121.8, 119.2, 119.1 (q, *J* = 4.2 Hz), 85.7, 46.0, 41.4, 29.6, 27.5, 25.6, 22.7, 14.0. IR (KBr): 3545, 2929, 2857, 1784, 1716, 1147, 699. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{21}H_{26}F_3NO_3Na^+$, 420.17484; found, 420.17570.

*(3S,4S)-tert-Butyl2-oxo-3-pentyl-4-phenyl-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3m**).* Colorless oil, 122.6 mg, 99%. R_f = 0.7 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +139.0 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 8.7 min (major), 11.5 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.25 (m, 3H), 7.18−7.16 (m, 2H), 6.32 (d, *J* = 6.9 Hz, 1H), 3.78−3.76 (m, 1H), 2.75 (q, *J* = 6.8 Hz, 1H), 1.62−1.58 (m, 1H), 1.58 (s, 9H), 1.41−1.35 (m, 2H), 1.28−1.25 (m, 4H), 1.24−1.21 (m, 1H), 0.87−0.83 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 150.0, 135.5, 130.8, 130.4, 130.1 (q, *J* = 34.9 Hz), 129.7, 129.0, 128.2, 128.0, 124.5, 121.7, 119.1 (q, *J* = 4.2 Hz), 119.0, 85.6, 45.9, 41.3, 31.7, 27.4, 27.0, 25.8, 22.4, 14.0. IR (KBr): 3566, 2932, 2859, 1783, 1716, 1146, 699. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{22}H_{28}F_3NO_3Na^+$, 434.19070; found, 434.19135.

*(3S,4S)-tert-Butyl3-heptyl-2-oxo-4-phenyl-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3n**).* Colorless oil, 141.5 mg, 99%. R_f = 0.7 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +84.9 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 8.1 min (major), 11.7 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.18 (m, 3H), 7.11−7.08 (m, 2H), 6.25 (d, *J* = 6.8 Hz, 1H), 3.70 (dd, *J* = 6.6, 5.5 Hz, 1H), 2.69 (q, *J* = 6.8 Hz, 1H), 1.59−1,48 (br, 11H), 1.33−1.28 (m, 2H), 1.21−1.15 (br, 9H), 1.07−1.04 (m, 1H), 0.80−0.76 (m, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 170.3, 150.0, 135.5, 130.8, 130.4, 130.1 (q, *J* = 34.9 Hz), 129.7, 129.0, 128.2, 128.0, 124.4, 121.7, 119.1, 119.0 (q, *J* = 4.1 Hz), 116.3, 85.6, 45.9, 41.3, 31.7, 29.4, 29.0, 27.4, 27.3, 25.8, 22.6, 14.1. IR (KBr): 3536, 2929, 2857, 1783, 1716, 1147, 699. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{24}H_{32}F_3NO_3Na^+$, 462.22187; found, 462.22265.

*(3S,4S)-tert-Butyl3-nonyl-2-oxo-4-phenyl-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3o**).* Colorless oil, 134.9 mg, 99%. R_f = 0.6 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +60.8 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 7.8 min (major), 10.4 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.18 (m, 3H), 7.09 (dd, *J* = 9.9, 8.3 Hz, 2H), 6.25 (d, *J* = 6.8 Hz, 1H), 3.70 (dd, *J* = 6.5, 5.5 Hz, 1H), 2.69 (q, *J* = 6.8 Hz, 1H), 1.59−1.50 (br, 10H), 1.48−1.28 (m, 2H), 1.21−1.15 (m, 14H), 1.06−1.04 (m, 1H), 0.79 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 150.0, 135.5, 130.8, 130.4, 130.1 (q, *J* = 34.9 Hz), 129.7, 129.0, 128.2, 128.0, 124.5, 121.7, 119.1 (q, *J* = 4.2 Hz), 119.0, 116.3, 85.6, 45.9, 41.3, 31.9, 29.5, 29.4, 29.3, 27.4, 27.3, 25.8, 22.7, 14.1. IR (KBr): 3566, 2961, 2935, 1784, 1716, 1146, 699. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{26}H_{36}F_3NO_3Na^+$, 490.25303; found, 490.25395.

*(3S,4S)-tert-Butyl3-decyl-2-oxo-4-phenyl-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3p**).* Colorless oil, 139.0 mg, 96%. R_f = 0.6 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +117.7 (*c* 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 7.8 min (major), 10.0 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.17 (m, 3H), 7.09(d, *J* = 6.5 Hz, 2H), 6.24 (d, *J* = 6.8 Hz, 1H), 3.69

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(t, J = 6.1 Hz, 1H), 2.68 (q, J = 6.8 Hz, 1H), 1.59−1.50 (br, 10), 1.44−1.27 (m, 2H), 1.19−1.15 (br, 16H), 1.08−1.03 (m, 1H), 0.79 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 150.0, 135.5, 130.8, 130.4, 130.1 (q, J = 35.0 Hz), 129.7, 129.0, 128.2, 128.0, 127.9, 121.7, 119.1 (q, J = 4.1 Hz), 119.0, 85.6, 45.9, 41.3, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 27.4, 27.3, 25.8, 22.7, 14.1. IR (KBr): 3545, 2929, 2857, 1784, 1716, 1147, 699. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{27}H_{38}F_3NO_3Na^+$, 504.26883; found, 504.26960.

*(3S,4S)-tert-Butyl 3-isobutyl-2-oxo-4-phenyl-6-(trifluoromethyl)-3,4-dihydropyridine-1(2H)-carboxylate (**3q**).* Colorless oil, 25.0 mg, 21%.R_f = 0.7 (hexane/EtOAc = 10:1), $[\alpha]_D^{20}$ +135.5 (c 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm hexane/i-PrOH = 95:5, 0.5 mL/min, 254 nm, 8.3 min (major), 10.3 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.14 (m, 5H), 6.25 (d, J = 6.9 Hz, 1H), 3.84 (t, J = 5.9 Hz, 1H), 2.46 (dd, J = 8.7, 6.3 Hz, 1H), 1.79−1.71 (m, 1H), 1.50 (s, 9H), 1.00 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 150.0, 136.3, 130.0,129.6 (d, J = 34.9 Hz), 129.0, 128.2, 127.9, 121.7, 119.8, 119.8 (d, J = 4.1 Hz). 119.0, 85.6, 52.3, 40.4, 27.4, 25.5, 22.0, 20.8. IR (KBr): 2982, 2934, 2874, 1782, 1713, 1144, 699. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{20}H_{24}F_3NO_3Na^+$, 406.16054; found, 406.16005.

Removal of *N*-Boc. The solution of cycloadduct **3a** (58 mg, 0.1 mmol) in 2 mL DCM containing TFA (113 uL, 1 mmol) was stirred vigorously at 0 °C for 15 min, followed by at room temperature for 15 min. The reaction mixture was washed with saturated aqueous $NaHCO_3$, and the aqueous layer was back-extracted with DCM (2 × 2 mL). The organic layer was combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography using 2% ethyl acetate in petroleum ether as eluent to afford the compound **4a** as a white solid, mp 147−150 °C, 32.0 mg, 99%. R_f = 0.7 (n-hexane/EtOAc = 5:1), $[\alpha]_D^{20}$ +298.9 (c 1.0, $CHCl_3$), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/i-PrOH = 95:5, 0.5 mL/min, 254 nm, 24.3 min (major), 26.3 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.22−7.11 (m, 6H), 7.02−6.97 (m, 4H), 5.84 (d, J = 6.3 Hz, 1H), 3.54 (t, J = 6.2 Hz, 1H), 3.25 (dd, J = 14.5, 5.0 Hz, 1H), 3.17−3.11 (m, 1H), 2.31−2.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 139.0, 137.2, 129.1, 128.9, 128.5, 128.3, 128.0, 127.9, 127.5, 127.2 (q, J = 35.2 Hz), 126.8, 126.4, 121.5, 118.8, 112.1 (q, J = 4.4 Hz), 112.1, 46.0, 40.4, 31.3. ^{19}F NMR (471 MHz, $CDCl_3$) δ −70.43 (s). IR (KBr): 3566, 3218, 2960, 1688, 1507, 1298, 698. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{19}H_{15}F_3NO^-$, 330.11038; found, 330.11003.

■ ASSOCIATED CONTENT

Supporting Information

X-ray data for cycloadduct **3h** (CIF), NMR, and HPLC spectra for obtained compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00232.

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Notes

The authors declare no competing financial interest.

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