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A Noncoordinating Acid–Base Catalyst for the Mild and Nonreversible *tert*-Butylation of Alcohols and Phenols

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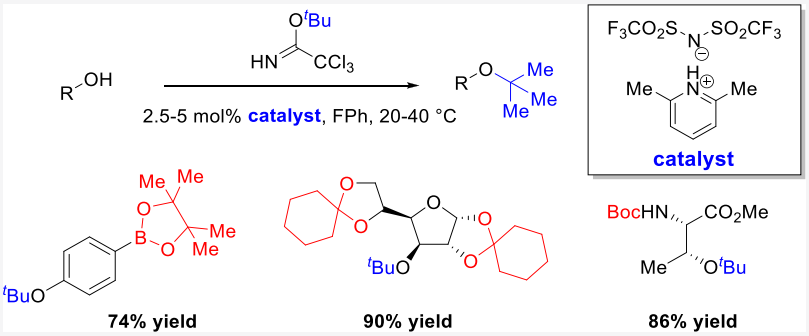

ABSTRACT: A mild and nonreversible *tert*-butylation of alcohols and phenols can be achieved in high yields using the noncoordinating acid–base catalyst [bis(trifluoromethane)sulfonimide and 2,6-lutidine] with a *tert*-butylation reagent, *tert*-butyl 2,2,2-trichloroacetimidate. This method allows the use of substrates containing acid sensitive groups such as ketal, Boc, and boronate esters.

The *tert*-butylation of alcohols is arguably one of the fundamental reactions of organic synthesis. The resulting *tert*-butyl ethers can serve as both a desired targeted substrate[1] but more commonly are employed as protecting groups. Although the *tert*-butyl ether is one of the few ethers stable under strongly basic conditions,[2] it is highly underutilized owing to the harsh conditions required for its synthesis.[3] The classical method for the *tert*-butyl ether synthesis involves the treatment of an alcohol substrate with a large excess of isobutylene and a strong acid catalyst.[4] Bartoli and co-authors have shown that metal perchlorates[5] are amenable for the catalytic *tert*-butylation of a number of diverse substrates employing Boc-anhydride as the *tert*-butyl source. Although the conditions are mild and amenable to acid sensitive functionality, the process still requires a metal catalyst and the known hazards of perchlorates preclude their use for large scale synthesis.[6] Considering the importance of the *tert*-butyl ether, a mild method for the synthesis of this important group is still needed. On the basis of the seminal work of Armstrong et al.,[7] *tert*-butyl trichloroacetimidate (**3**) can be used in the presence of a catalytic amount of Lewis acid boron trifluoride etherate to get access to the *tert*-butyl ethers using alcohol substrates to afford moderate to good yields. In addition, the groups of Albiniak,[8] Kunishima[9] and others[10] have developed the *tert*-butylation conditions using the alternative reagents; however, an efficient and mild protocol with wide substrate scope is yet to be realized.

During our development work for the synthesis of the atropisomeric HIV integrase inhibitor, we developed an efficient and mild method for the late-stage installment of the requisite *tert*-butyl ether (Figure 1).[11] The targeted compound (**2**) possessed a *tert*-butyl ether embedded within a sterically crowded environment. Furthermore, the substrate possessed two basic residues that complicated the synthesis of the *tert*-butyl ether as most methods are based on strong protic acid promoters. Through extensive investigation, we were able to identify bis(trifluoromethane)sulfonimide as a suitable catalyst for the *tert*-butyl ether formation.[12] As this catalyst system possessed a number of advantages, including being mild, nonreversible, and stable even at elevated temperatures, we wished to expand on this finding. However, initial attempts at the *tert*-butylation with the model substrate phenol **4** proceeded in no conversion with the conditions from our initial discovery[11] (Figure 1). Considering the inherent advantages found in the original system, the application of this process in a general manner would offer significant

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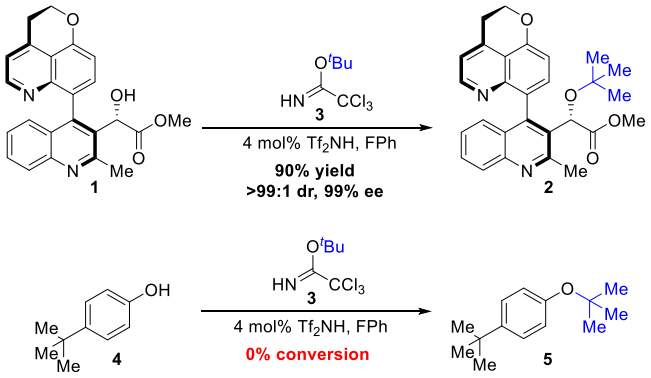


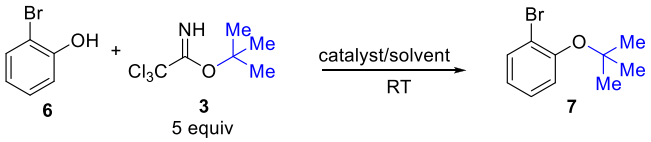
Figure 1. Installation of the *tert*-butyl ether in the synthesis of an HIV integrase inhibitor catalyzed by bis(trifluoromethane)sulfonimide. Initial attempt at the *tert*-butylation of a model substrate **4**.

benefits. Herein, we wish to report the development of a noncoordinating acid–base catalyst for the mild and non-reversible *tert*-butylation of alcohols and phenols.

We decided to systematically explore the variables for the *tert*-butylation with a more hindered model substrate: 2-bromophenol **6** (Table 1). Control experiments lacking a catalyst proceeded in no conversion (Table 1, entry 1). As observed with the model phenol **4**, no conversion was observed employing our previously reported conditions for the HIV integrase inhibitor with the catalyst bis-(trifluoromethane)sulfonimide (Table 1, entry 2). Informatively, upon the addition of the acid catalyst to the reaction mixture possessing the *tert*-butylating reagent **3**, the reaction instantly bubbled violently, indicating a rapid decomposition of the reactive reagent, liberating isobutylene gas (Figure 2). This can be a safety concern when performing an experiment or scaling up (proper vent must be used) and emphasizes the need for milder reaction conditions.

As the results suggested, strong acids have a detrimental effect to reaction efficiency. The *tert*-butyl cation could as well serve as a strong acid for the reactive *tert*-butylating agent presumably through an autocatalytic pathway (Figure 2). The acid would then need to be modulated with a suitable noncoordinating base to avoid the alternative decomposition pathway where the base (nucleophilic species) could competitively trap the *tert*-butyl cation (Nuc pathway Figure 2). Initial attempts to modulate the strong acid with the hindered triethylamine or Hünig's base proceeded in no detectable conversion (Table 1, entries 3 and 4). Referring back to our initial discovery with the HIV integrase inhibitor (Figure 1) where the substrate possessed two sterically demanding basic pyridine groups, we hypothesized that the product and/or starting material itself was serving as the sought after base to modulate the strong acid for this reaction. Employing a mimic of the substrate, the hindered 2,6-di-*tert*-butyl-4-methyl pyridine or the less expensive 2,6-lutidine, the reactivity was restored and high conversion was observed even with the hindered model substrate (Table 1, entries 5 and 6). As observed previously with our initial system, fluorobenzene or dichloromethane are well suited for this chemistry, while other solvents suffered from a significant decrease in efficiency (Table 1).

Table 1. Development of the Acid–Base Catalyst for the *tert*-Butylation of Phenol 6 with 3



Entry	Acid	Base	Solvent	Time	Conversion[a]
1	None	None	FPh	15 h	<1%
2	Tf_2NH (5 mol%)	None	FPh	15 h	<1%
3	Tf_2NH (5 mol%)	Et_3N (1.0 equiv)	FPh	15 h	<1%
4	Tf_2NH (5 mol%)	$^iPr_2EtN$ (1.0 equiv)	FPh	15 h	<1 %
5	Tf_2NH (5 mol%)	2,6-di-^{t}Bu-4-MePyr (10 mol%)	FPh	15 h	83%
6	Tf_2NH (5 mol%)	2,6-lutidine (0.5 to 1.0 equiv)	FPh	15 h	81%
7	Tf_2NH (5 mol%)	2,6-lutidine (0.5 equiv)	DCM	15 h	71%
8	Tf_2NH (5 mol%)	2,6-lutidine (0.5 equiv)	THF	15 h	12%
9	Tf_2NH (5 mol%)	2,6-lutidine (0.5 equiv)	THF/C_6H_{12}	15 h	22%
10	Tf_2NH (5 mol%)	2,6-lutidine (0.5 equiv)	*t*BuOAc	15 h	39%
11	Tf_2NH (5 mol%)	2,6-lutidine (0.5 equiv)	MTBE	15 h	26%
12	Tf_2NH (5 mol%)	2,6-lutidine (0.5 equiv)	Toluene	15 h	26%
13	Tf_2NH (5 mol%)	2,6-lutidine (0.5 equiv)	MeTHF	15 h	11%
14	Tf_2NH (5 mol%)	2,6-lutidine (0.5 equiv)	IPAc	15 h	41%

[a]Conversion determined as molar conversion via HPLC analysis.

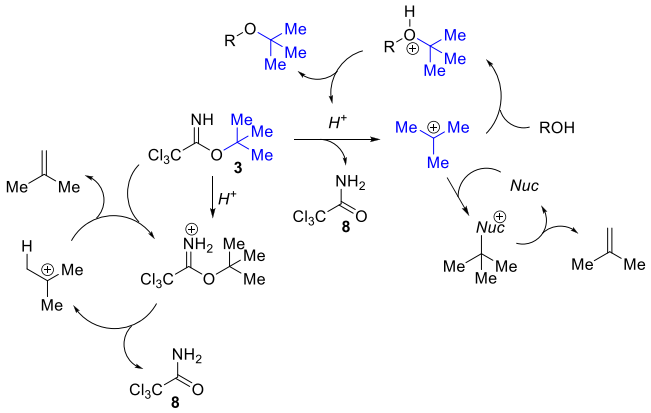
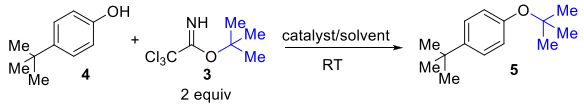


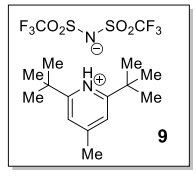
Figure 2. Proposed productive and nonproductive catalytic cycles for the *tert*-butylation.

The less sterically demanding phenol **4** was used to verify this result while also serving as a benchmark. The control experiments with no catalyst or just the strong acid proceeded in no conversion (Table 2, entries 1–3). With a preformed catalyst **9**, near complete conversion was observed (96%) with only 2.0 equiv of the *tert*-butylating reagent (Table 2, entry 4). Employing the standard conditions as reported by Armstrong[7] (50 mol % boron trifluoride) provided only 19% conversion to the desired product (Table 2, entry 6). Furthermore, the noncoordinating acid–base catalyst **9** was shown to be

Table 2. Development of the Acid–Base Catalyst for the *tert*-Butylation of Phenol 4 with 3



Entry	Catalyst	Solvent	Time	Conversion[a]
1	None	FPh	15 h - 3d	0%
2	None	DCM	15 h - 3d	0%
3	Tf_2NH (5 mol%)	FPh	1 to 15h	<1%
4	**9** (5 mol%)	FPh	45 min	96%
5	**9** (5 mol%)	DCM	45min	74%
6	BF_3•OEt_2 (50 mol%)	FPh	15h - 2d	19%
7	PPTS (10 mol%)	FPh	3h - 2d	60%



[a]Molar conversion as determined by HPLC analysis.

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superior as compared to the commercially available PPTS (60% conversion, Table 2, entry 7).

After deriving the acid–base system which is based on a highly noncoordinating modulated acid catalyst, a number of phenolic substrates were tested under the optimized conditions (Figure 3). The modulated acid–base catalyst performed well

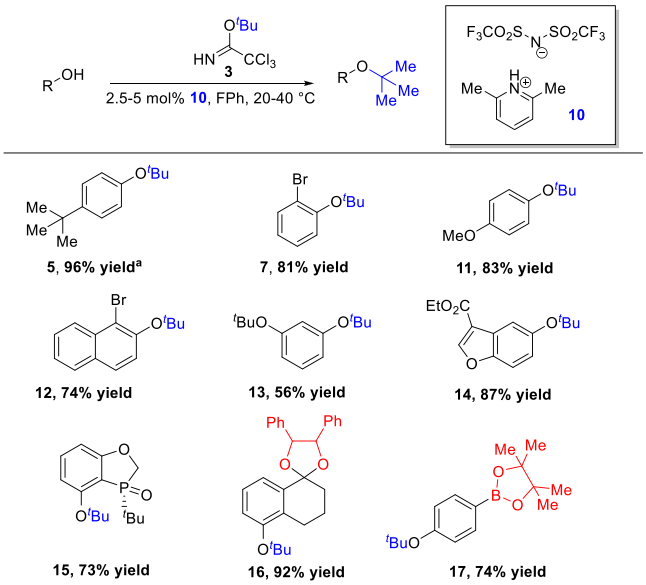

Figure 3. Phenolic substrate exploration for the *tert*-butylation employing the acid–base catalyst **10**. [a]Catalyst **9** was used.

for a series of phenol substrates, providing good to excellent isolated yields. For the more hindered substrates leading to **15**[13,14] and **16**, additional equivalents of the *tert*-butylating reagent were utilized.[15] In fact, for all examples shown below, the *tert*-butylating reagent could be titrated into the reaction as the catalyst is stable over long periods (up to 1 week at 40 °C) as shown in the initial HIV integrase inhibitor that the hindered basic pyridine is viable in this chemistry.

To further test the mild nature of the acid–base catalyst, the corresponding phenols possessing the acid sensitive acetal **16** and pinacol boronate **17** were tested in the *tert*-butylation process. No detectable destruction of the acid sensitive groups was observed, and both substrates can be isolated in high yield (74–92%).

More challengingly, terpene substrates were also amenable, providing the desired products cleanly in up to 91% yield (Figure 4, **18**–**20**). Only the product and unreacted starting material were observed in the case where the conversion was moderate (i.e., **19**).

With the success of these substrates, we turned our attention to acid sensitive compounds, in particular, to the Boc protected alcohols.[9] A number of Boc protected substrates were examined with the developed methodology, and the less hindered secondary alcohol **21** was isolated in 83% yield. The Boc protected amino acids hydroxyl-proline **25**[16] and other hydroxyl esters (**23**,[17] **24**, **26**) were also found to be stable under the reaction conditions, affording high yields of the corresponding *tert*-butyl ether products (76–90%).

In summary, we have developed a novel noncoordinating acid–base catalyst for the mild and nonreversible *tert*-butylation of a variety of aliphatic alcohols and phenols containing acid sensitive groups such as ketal and pinacol

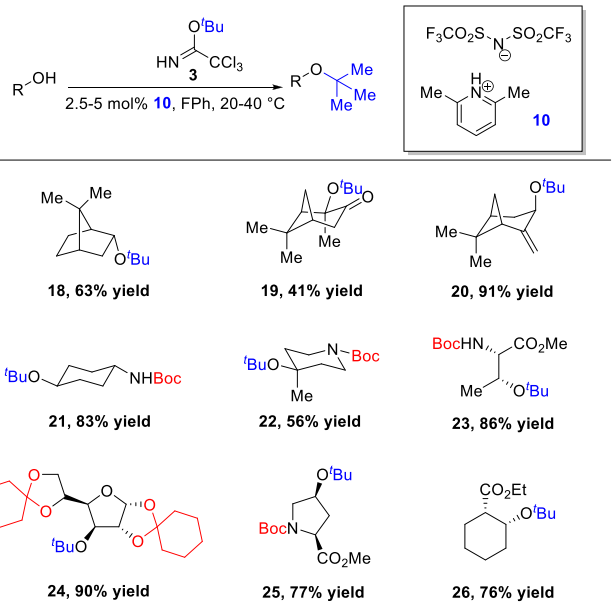

Figure 4. Aliphatic substrate exploration for the *tert*-butylation employing the acid–base catalyst **10**.

boronate to provide corresponding *tert*-butyl ethers in good to excellent yields. Most reactions were run at room temperature, and this methodology was successfully demonstrated on various natural product type alcohol substrates (Figure 4). Therefore, the present method provides an efficient and mild protocol to a wide range of *tert*-butyl ether products, which we believe will provide great utility to the chemistry community.

EXPERIMENTAL SECTION

General. All reactions were performed under anhydrous conditions unless otherwise stated with oven-dried glassware and under an argon atmosphere. All starting materials and reagents were purchased from commercial sources and used as received unless otherwise noted. Anhydrous solvents were purchased from Alfa Aesar, Aldrich, or Fisher and used without further purification, but with a specification of <200 ppm water as determined by Karl Fisher analysis. HPLC analysis was performed on an Agilent 1100 quaternary pump HPLC equipped with a Halo Rp-amide, 4.6 × 150 mm column eluted with a acetonitrile and water system. Flash chromatography was performed on a Combi-Flash system with silica column cartridges using gradient 0–20% ethyl acetate in hexanes solvent system. TLC was performed on EMD silica gel F254 2.5 × 7.5 cm plates and visualized with UV (254 nm) or with a potassium permanganate stain. NMR analysis was conducted on a Bruker 400 or 500 MHz instrument, and the spectra were calibrated to the internal standard TMS or residual solvent: $CDCl_3$ (^{1}H NMR δ 7.26 ppm and ^{13}C{1H} NMR δ 77.16 ppm) with the corresponding splitting designations (s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, br = broad). High resolution mass spectrometric data were obtained on a Thermo LTQ-FT Ultra HPLC/MS spectrometer (DART) or Agilent LC-TOF/MS spectrometer (ESI).

General Procedure for Synthesis of *tert*-Butyl Ethers. To a 2 dram (7.5 mL) vial was charged 0.200 g of an alcohol or a phenol (2-bromophenol, 1.156 mmol, 1.00 equiv) and fluorobenzene (2.00 mL). To the resulting mixture was charged a solution of catalyst **10** prepared in a Glovebox from 2,6-lutidine (0.062 g, 0.578 mmol, 0.5 equiv) and bis(trifluoromethane)sulfonimide (0.012 g, 0.029 mmol, 0.025 equiv). To the batch was charged *tert*-butyl-2,2,2-trichloroacetimidate (TBTA) (**3**) (1.263 g, 1.03 mL, 5.780 mmol, 5.0 equiv) dropwise over the course of 15 min, and the batch was allowed to run at 20 °C for 15 h, at which point HPLC analysis indicated full consumption of 2-bromophenol. The sample was filtered through a

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silica plug. The plug was washed with 5 mL of dichloromethane, and the combined organic filtrates were concentrated under reduced pressure. The resulting mixture was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) to produce 215 mg (81% yield) of *1-bromo-2-(tert-butoxy) benzene* (**7**) as a colorless oil. The spectroscopic data match those reported previously.[18] ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.55 (dd, J = 7.8, 1.8 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.12 (d, J = 8.0, 1.5 Hz, 1H), 6.91 (td, J = 7.6, 1.2 Hz, 1H), 1.44 (s, 9H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 153.5, 133.47, 127.9, 124.3, 124.0, 119.3, 81.4, 29.2.

*1-(tert-Butoxy)-4-(tert-butyl)benzene (**5**).* 5.0 mol % catalyst **9** and 2.0 equiv of **3** were used, and the reaction mixture was allowed to stir at 20 °C for 45 min. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless oil in 264 mg (96% yield). The spectroscopic data match those reported previously.[19] ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.25 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 1.33 (s, 9H), 1.30 (s, 9H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 153.0, 146.0, 125.7, 123.6, 78.1, 34.4, 31.7, 29.0.

*1-(tert-Butoxy)-4-methoxybenzene (**11**).* 5.0 mol % catalyst **10** was used, and the reaction mixture was allowed to stir at 40 °C (using an oil bath) for 18 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless liquid in 241 mg (83% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.92 (dt, J = 9.0, 2.9 Hz, 2H), 6.79 (dt, J = 9.0, 3.0 Hz, 2H), 3.77 (s, 3H), 1.30 (s, 9H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 155.9, 148.7, 125.4, 113.9, 78.1, 55.6, 28.8. HRMS (DART): m/z calcd for $C_{11}H_{17}O_2$ $[M + H]^+$: 181.1223, found: 181.1225.

*1-Bromo-2-tert-butoxynaphthalene (**12**).* The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a yellow oil in 185 mg, (74% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.25 (d, J = 8.5 Hz, 1 H), 7.81 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.61−7.58 (m, 1H), 7.48−7.44 (m, 1H), 7.37 (d, J = 8.5 Hz, 1H), 1.54 (s, 9H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 151.6, 133.4, 131.2, 128.0, 127.4, 127.2, 125.1, 123.7, 117.2, 81.9, 29.5. HRMS (ESI): m/z calcd for $C_{14}H_{16}O_1Br_1$ $[M + H]^+$: 279.0379, found: 279.0370.

*1,3-Bis(tert-butoxy)benzene (**13**).* The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a yellow oil in 150 mg (74% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.11 (t, J = 8.3 Hz, 1H), 6.72 (dd, J = 8.0, 2.5 Hz, 1H), 6.65 (t, J = 2.3 Hz, 1H), 1.32 (s, 18H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 155.9, 128.4, 120.4, 119.4, 78.5, 29.0. HRMS (ESI): m/z calcd for $C_{14}H_{23}O_2$ $[M + H]^+$: 223.1693, found: 223.1699.

*Ethyl 5-(tert-Butoxy)benzofuran-3-carboxylate (**14**).* 5.0 mol % catalyst **10** was used, and the reaction mixture was allowed to stir at 40 °C (using an oil bath) for 18 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless oil in 221 mg (87% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.21 (s, 1H), 7.67 (d, J = 2.0 Hz, 1H),), 7.37 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 4.38 (q, J = 5.8 Hz, 2H), 1.39 (d, J = 7.2 Hz, 3H), 1.36 (s, 9H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 163.4, 152.24, 152.16, 151.6, 125.1, 122.6, 116.7, 114.9, 111.5, 78.7, 60.5, 28.9, 14.4. HRMS (DART): m/z calcd for $C_{15}H_{19}O_4$ $[M + H]^+$: 263.1278, found: 263.1278.

*Phosphine **15**.* 15.0 equiv of **3** was used, and the reaction mixture was allowed to stir at 20 °C for 20 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a white solid in 182 mg (73% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.31 (t, J = 8.2 Hz, 1H), 6.66 (dd, J = 6.6, 4.3 Hz, 1H), 6.54 (dd, J = 6.6, 3.3 Hz, 1H), 4.48 (dd, J = 11.0, 2.3 Hz, 1H), 4.33 (dd, J = 11.2, 11.0 Hz, 1H), 1.50 (s, 9H), 1.23 (d, J = 16.0 Hz, 9H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 166.6 (d, J = 17.5 Hz), 158.9 (d, J = 2.5 Hz), 135.7 (d, J = 1.3 Hz), 112.5 (d, J = 5.8 Hz), 107.4 (d, J = 92.3 Hz), 107.2 (d, J = 5.5 Hz), 81.3, 66.0 (d, J = 60.0 Hz), 34.1 (d, J = 72.5 Hz), 29.2, 24.8 (d, J = 1.3 Hz). ^{31}P NMR ($CDCl_3$, 202 MHz) δ: 63.4. HRMS (DART): m/z calcd for $C_{15}H_{24}O_3P_1$ $[M + H]^+$: 283.1458, found: 283.1458.

*5′-(tert-Butoxy)-4,5-diphenyl-3′,4′-dihydro-2′H-spiro[1,3-dioxolane-2,1′-naphthalene] (**16**).* 20.0 equiv of **3** was used. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a white solid in 213 mg (92% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (dd, J = 7.8, 1.0 Hz, 1H), 7.34−7.31 (m, 8H), 7.27−7.22 (m, 3H), 7.04 (dd, J = 8.0, 1.2 Hz, 1H), 5.09 (d, J = 8.8 Hz, 1H), 4.92 (d, J = 8.8 Hz, 1H), 2.89−2.81 (m, 1H), 2.75−2.67 (m, 1H), 2.32−2.28 (m, 2H), 2.08−2.00 (m, 2H), 1.42 (s, 9H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz) δ: 153.8, 139.4, 137.8, 136.3, 133.1, 128.7, 128.6, 128.5, 128.2, 127.2, 126.6, 126.2, 120.9, 120.7, 108.2, 86.7, 85.3, 35.4, 29.5, 28.2, 24.5, 20.5. HRMS (ESI): m/z calcd for $C_{28}H_{31}O_3$ $[M + H]^+$: 415.2268, found: 415.2244.

*2-[4-(tert-Butoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**17**).* 7.0 equiv of **3** was used, and the reaction mixture was allowed to stir at 20 °C for 24 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a white solid in 186 mg (74% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.74 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 1.36 (s, 9H), 1.33 (s, 12H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 158.5, 135.8, 123.0, 83.6, 78.6, 29.0, 24.9. HRMS (ESI): m/z calcd for $C_{16}H_{26}O_3$ B_1 $[M + H]^+$: 277.1970, found: 277.1975.

*(1S,2R,4S)-2-(tert-Butoxy)-1,7,7-trimethylbicyclo[2.2.1]heptane (**18**).* 7.0 equiv of **3** was used, and the reaction mixture was allowed to stir at 20 °C for 24 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless oil in 176 mg (63% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.66−3.63 (m, 1 H), 2.12−2.06 (m, 1H), 2.04−1.99 (m, 1H), 1.69−1.63 (m, 1H), 1.58−1.56 (m, 1H), 1.25−1.20 (m, 1H), 1.14−1.09 (m, 1H), 1.11 (s, 9H), 0.93 (dd, J = 10.2, 2.6 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 76.0, 72.4, 49.1, 47.1, 45.6, 40.2, 28.8, 28.5, 26.7, 20.1, 19.1, 13.7. HRMS (DART): m/z calcd for $C_{14}H_{27}O_1$ $[M + H]^+$: 211.2056, found: 211.2057.

*(1R,2R,5R)-2-(tert-Butoxy)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one (**19**).* 11.0 equiv of **3** was used. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a light yellow liquid in 109 mg (41% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.65−2.55 (m, 2H), 2.41−2.36 (m, 1H), 2.19 (t, J = 6.2 Hz, 1H), 2.08−2.05 (m, 1H), 1.95 (d, J = 10.5 Hz, 1H), 1.43 (s, 3H), 1.32 (s, 3H), 1.25 (s, 9H), 0.82 (s, 3H). ^{13}C{1H} NMR ($CDCl_3$, 125 MHz) δ: 212.1, 117.5, 81.8, 76.5, 53.1, 44.7, 39.1, 31.0, 29.5, 28.0, 24.4, 22.6. HRMS (DART): m/z calcd for $C_{14}H_{25}O_2$ $[M + H]^+$: 225.1849, found: 225.1850.

*(1S,3R,5S)-3-(tert-Butoxy)-6,6-dimethyl-2-methylidenebicyclo-[3.1.1]heptane (**20**).* 5.0 mol % catalyst **10** was used, and the reaction mixture was allowed to stir at 40 °C (using an oil bath) for 40 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless oil in 249 mg (91% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.94 (t, J = 1.4 Hz, 1H), 4.82 (t, J = 1.4 Hz, 1H), 4.25 (dd, J = 8.1, 1.3 Hz, 1H), 2.51 (t, J = 5.6 Hz, 1H), 2.40−2.34 (m, 1H), 2.28−2.21 (m, 1H), 1.97−1.93 (m, 1H), 1.85 (ddd, J = 14.1, 3.9, 1.9 Hz, 1H), 1.57 (d, J = 9.6 Hz, 1H), 1.25 (s, 12H), 0,70 (s, 3H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz) δ: 154.8, 111.5, 73.9, 66.0, 51.5, 40.3, 40.0, 37.5, 29.0, 28.8, 26.0, 22.2. HRMS (DART): m/z calcd for $C_{14}H_{25}O$ $[M + H]^+$: 209.1900, found: 209.1901.

*tert-Butyl (1R,4R)-4-tert-Butoxycyclohexylcarbamate (**21**).* 11.0 equiv of **3** was used. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a white solid in 209 mg (83% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.45 (bs, NH, 1H), 3.27−3.21 (m, 2H), 1.88−1.86 (m, 2H), 1.70−1.68 (m, 2H), 1.33 (s, 9H), 1.28−1.10 (m, 2H), 1.10 (s, 9H), 1.10−1.02 (m, 2H). ^{13}C{1H} NMR ($CDCl_3$, 126 MHz) δ: 155.2, 78.9, 73.2, 69.3, 48.9, 33.7, 31.8, 28.4, 28.3. HRMS (ESI): m/z calcd for $C_{15}H_{30}O_3N_1$ $[M + H]^+$: 272.2220, found: 272.2221.

*tert-Butyl 4-(tert-Butoxy)-4-methylpiperidine-1-carboxylate (**22**).* 20.0 equiv of **3** was used. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a light yellow oil in 141 mg (56% yield). ^{1}H NMR

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($CDCl_3$, 500 MHz) δ 3.60 (bs, 2 H), 3.21 (t, J = 11.3 Hz, 2H), 1.70−1.68 (m, 2H), 1.36−1.32 (m. 2H), 1.41 (s, 9H), 1.28 (s, 3H), 1.24 (s, 9H). $^{13}C\{1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 155.1, 79.1, 74.2, 72.4, 39.7, 31.8, 28.6, 28.1, 27.8. HRMS (ESI): m/z calcd for $C_{15}H_{30}O_3N_1$ $[M + H]^+$: 272.2220, found: 272.2223.

*Methyl (2S,3R)-3-(tert-Butoxy)-2-{[(tert-butoxy)carbonyl]amino}-butanoate (**23**).* 5.0 mol % catalyst **10** was used, and the reaction mixture was allowed to stir at 40 °C (using an oil bath) for 40 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless oil in 213 mg (86% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.30−5.27 (m, 1H), 4.20−4.13 (m, 2H), 3.69 (s, 3H), 1.44 (s, 9H), 1.19 (d, J = 6.0 Hz, 3H), 1.09 (s, 9H). $^{13}C\{1H\}$ NMR ($CDCl_3$, 100 MHz) δ: 172.1, 156.4, 79.8, 74.1, 67.6, 59.5, 52.2, 28.5, 28.4, 21.0. HRMS (DART): m/z calcd for $C_{14}H_{28}O_5N_1$ $[M + H]^+$: 290.1962, found: 290.1962.

*(3a′R,5′R,6′S,6a′R)-6′-(tert-Butoxy)-5′-{(R)-1,4-dioxaspiro[4.5]-decan-2-yl}-tetrahydrospiro[cyclohexane-1,2′-furo[2,3-d][1,3]-dioxole] (**24**).* 5.0 mol % catalyst **10** was used, and the reaction mixture was allowed to stir at 40 °C (using an oil bath) for 40 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless oil in 210 mg (90% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.86 (d, J = 3.6 Hz, 1H), 5.30 (s, 1H), 4.39 (d, J = 3.6 Hz, 1H), 4.31−4.26 (m, 1H), 4.10−4.06 (m, 3H), 3.98−3.94 (m, 1H), 1.72−1.36 (m, 19H), 1.24 (s, 9H). $^{13}C\{1H\}$ NMR ($CDCl_3$, 100 MHz) δ: 112.2, 109.4, 104.8, 85.1, 81.3, 75.0, 74.8, 71.9, 67.0, 36.52, 36.45, 35.8, 34.9, 28.2, 25.3, 25.0, 24.1, 23.92, 23.86, 23.6. HRMS (DART): m/z calcd for $C_{22}H_{37}O_6$ $[M + H]^+$: 397.2585, found: 397.2586.

*(2S,4S)-4-tert-Butoxy-pyrrolidine-1,2-dicarboxylic Acid 1-tert-Butyl Ester 2-Methyl Ester (**25**).* 5.0 mol % catalyst **10** was used. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless oil in 189 mg (77% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.33−4.19 (m, 1H), 4.16−4.10 (m, 1H), 3.74−3.59 (m, 1H), 3.70 (s, 3H), 3.25−3.20 (m, 1H), 2.40−2.29 (m, 1H), 2.01−1.95 (m, 1H), 1.46 (br s, 3H), 1.40 (br s, 6H), 1.16 (s, 9H). $^{13}C\{1H\}$ NMR ($CDCl_3$, 100 MHz) δ: 173.4, 153.8, 80.1, 74.0, 69.5, 68.7, 57.7, 57.4, 53.4, 52.7, 52.0, 38.6, 38.0, 28.6, 28.43, 28.37, 28.35. HRMS (DART): m/z calcd for $C_{15}H_{28}O_5N_1$ $[M + H]^+$: 302.1962, found: 302.1966.

*Ethyl (1S,2R)-2-(tert-Butoxy)cyclohexane-1-carboxylate (**26**).* 5.0 mol % catalyst **10** was used, and the reaction mixture was allowed to stir at 40 °C (using an oil bath) for 36 h. The product was purified by flash silica gel chromatography (gradient 0−20% ethyl acetate in hexanes) and obtained as a colorless liquid in 202 mg (76% yield). ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.16−4.13 (m, 1H), 4.11−3.99 (m, 2H), 2.37 (d, J = 11.0 Hz, 1H), 1.92−1.83 (m, 2H), 1.72−1.65 (m, 2H), 1.59−1.56 (m, 1H), 1.46−1.42 (m, 1H), 1.37−1.33 (m, 2H), 1.26−1.23 (m, 3H), 1.11 (s, 9H). $^{13}C\{1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 174.2, 73.2, 67.9, 60.0, 48.3, 32.8, 28.7, 24.4, 23.2, 20.7, 14.4. HRMS (ESI): m/z calcd for $C_{13}H_{24}O_3Na_1$ $[M + Na]^+$: 251.1623, found: 251.1619.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00193.

All associated ^1H NMR and $^{13}C\{1H\}$ NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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