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Development of a Phase-Transfer-Catalyzed, [2,3]-Wittig Rearrangement

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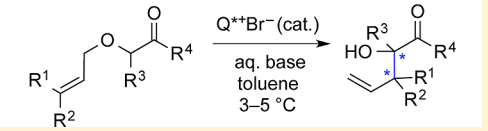
Supporting Information

ABSTRACT: An investigation into the use of phase-transfer catalysis for the [2,3]-sigmatropic rearrangement of allyloxy carbonyl compounds is described. Initial studies focused on identifying viable substrate classes that would undergo selective [2,3]-rearrangement under phase-transfer catalysis. Under certain conditions, the [2,3]-sigmatropic rearrangement of allyloxy carbonyl compounds takes place in the presence of a phase-transfer agent, providing a rare example of a phase-transfer-catalyzed unimolecular reaction. In the course of this investigation, it was found that catalysis is dependent on several variables including base concentration, catalyst structure, and substrate lipophilicity. Preliminary testing of chiral, nonracemic phase-transfer catalysts has shown promising levels of enantioselectivity for future development.

phase-transfer catalyzed, [2,3]-sigmatropic rearrangement



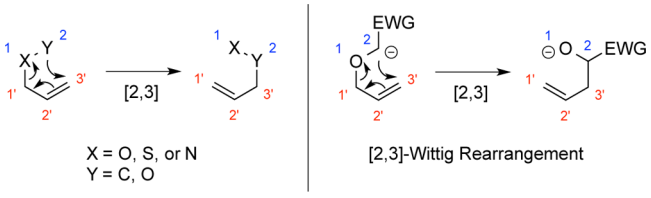
1. INTRODUCTION

Sigmatropic rearrangements represent one of the most powerful methods for the stereocontrolled synthesis of small molecules.[1,2] Because of the pericyclic nature of sigmatropic rearrangements, these reactions are completely atom economical and have the potential to rapidly build molecular complexity in a single step. The stereochemical outcome of these rearrangements is predictable as the reaction proceeds through a highly ordered, cyclic transition state.[3,4] The combination of catalysis and sigmatropic rearrangements has been used with great success in the development of reaction cascades that can build complex organic structures.[5,6] The ability to design catalysts that not only promote a given rearrangement but also control the enantioselectivity of these processes has been a long-standing goal in the field of asymmetric catalysis. The results presented herein are an account of our work in this area to use phase-transfer catalysis (PTC) as a means to catalyze and control the enantioselectivity of an anionic [2,3]-sigmatropic rearrangement.

2. BACKGROUND

2.1. [2,3]-Wittig Rearrangement and Stereoselection. The [2,3]-sigmatropic rearrangement is a thermal isomerization reaction involving six electrons and five atoms (Scheme 1, left). The numerical nomenclature ([2,3]) follows the naming convention used for other sigmatropic rearrangements by starting at the σ-bond that is breaking and counting to the position of the newly formed σ-bond (shown in blue and red). The [2,3]-rearrangement typically occurs at lower temperature than the well-studied [3,3]-rearrangement and is a thermally allowed suprafacial process in accordance with the Woodward–Hoffmann rules.[7] Substrates that undergo [2,3]-rearrangement can vary in substitution but typically consist of an allyl group and heteroatom substitution at either the X position, Y position, or both. Well-studied substrate classes that undergo [2,3]-rearrangement include allyl-substituted ylides, allyl sulfoxides, allyl selenoxides, and α-allyloxy carbanions.[8] The latter case is termed the [2,3]-Wittig rearrangement and is the focus of this investigation (Scheme 1, right).[9]

Scheme 1



The [2,3]-Wittig rearrangement is typically promoted by stoichiometric deprotonation or lithium–halogen exchange at the methylene adjacent to an allyloxy group. As a pericyclic reaction, the stereochemical outcome of the [2,3]-Wittig rearrangement is predictable and is rationalized by minimizing pseudo-1,3-diaxial strain within an envelope-shaped five-membered cyclic transition state.[10] The utility of the [2,3]-Wittig rearrangement in asymmetric synthesis stems from the potential to create two new stereocenters and a geometrically defined double bond based upon the configuration of a starting, enantioenriched allylic alcohol. The stereogenic center in the starting allyl ether dictates a single conformation of the five-membered ring transition state, leading to the [2,3]-rearrangement product as a single stereoisomer. This approach to acyclic stereocontrol has been used to great success in the synthesis of natural products[1,11] but is less applicable to substrates

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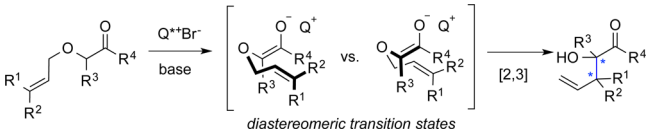
containing substitution at the position undergoing deprotonation. As a result, alternative approaches to stereocontrol have been investigated.

Auxiliary controlled, diastereoselective [2,3]-Wittig rearrangements are numerous, including the use of chiral moieties attached through amide,[12] ester,[13] or hydrazone[14] functional groups. In addition, the use of chiral boron enolates,[15] deprotonation by a chiral base,[16] and complexation of the organolithium intermediate with a chiral ligand[17] represent successful strategies that employ stoichiometric amounts of modifiers that are not directly attached to the substrate. Catalytic, enantioselective methods, however, are rare.[18] To date, only two examples of catalytic, enantioselective [2,3]-Wittig rearrangements have been reported: (1) enamine catalysis[19] and (2) metal-catalyzed formation of an allylic oxonium ylide followed by sigmatropic rearrangement.[20] In 2006, Gaunt reported a single example of an enantioselective [2,3]-rearrangement by using a chiral diamine organocatalyst, albeit in modest enantioselectivity (er 80:20) and diastereoselectivity (dr 2:1).[21] Examples of high enantioselectivities (er > 97:3) using chiral Rh catalysts for the metal-catalyzed formation of allylic oxonium ylides have been described by Doyle[22] and Hashimoto.[23] A more recent example from Davies reports a wider scope of substrate.[24] The authors propose that to obtain a high proportion of [2,3]-rearrangement, rather than OH-insertion, donor−acceptor metallocarbenes must be used as other metallocarbenes fail to proceed through the desired pathway. High enantioselectivities and moderate yields are obtained for a relatively narrow range of substrates in the reaction of styrenyl-substituted diazo acetates and substituted allylic alcohols.

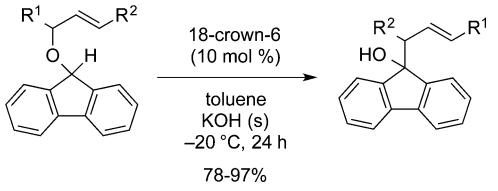
A general method for the catalytic, enantioselective [2,3]-Wittig rearrangement has yet to be reported. Although the examples in the preceding section represent good first steps, these methods are far from ideal in terms of both yield and substrate scope. In view of the anionic intermediates involved, we were intrigued by the possibility of using phase-transfer catalysis for the [2,3]-rearrangement of allyloxy carbonyl compounds. By employing a chiral, nonracemic quaternary ammonium catalyst, it is proposed that a chiral ammonium enolate intermediate could control the stereochemical course of the rearrangement by orienting the allyloxy group to either face of the enolate (Scheme 2). A phase-transfer-catalyzed enantioselective [2,3]-rearrangement has the potential to be operationally simple and applicable to a broader scope of substrates than the existing methods.

Scheme 2



2.2. Application of Phase-Transfer Catalysis to Intramolecular Reactions. The application of phase-transfer catalysis to sigmatropic rearrangements has been addressed in a single report from Yamamoto.[25] The authors report catalysis of the [2,3]-Wittig rearrangement of substituted 9-(allyloxy)-fluorenyl ethers under solid−liquid phase-transfer conditions (Scheme 3). Both crown ethers and quaternary ammonium salts function as catalysts, and no rearrangement is observed in

Scheme 3



their absence. No reaction is observed under liquid−liquid PTC conditions using 20% aq KOH. This process appears to proceed by a sigmatropic rearrangement in view of the following observations: (1) methyl substitution at the R^1 position results in exclusive formation of an *E*-double bond and (2) crotyl substrates (R^2 = Me) give the expected [2,3] rearrangement product with the methyl group located at the internal position. The authors observe competitive [1,2]-Wittig rearrangement at higher temperatures (approximately 5−10%), which is diminished by performing the reaction at −20 °C.

The initial report by Yamamoto indicates that *catalysis* of a molecular rearrangement is possible using phase-transfer catalysis. The question remains if a chiral, nonracemic quaternary ammonium salt could be effective in controlling the enantioselectivity. Asymmetric phase-transfer catalysis has rarely been applied to intramolecular reactions, perhaps due to the difficulty in biasing the conformations of the internal electrophile.[26] Nevertheless, three enantioselective intramolecular phase-transfer-catalyzed reactions have been reported. The first is an enantioselective, intramolecular Michael addition reported by Bandini (Scheme 4, eq 1).[27a] High enantioselectivity is obtained for a narrow class of substrates, and the authors propose a crucial hydrogen-bonding interaction between the hydroxyl group on the catalyst and the amide carbonyl group.[27b] Two other applications of asymmetric phase-transfer catalysis in the intramolecular asymmetric alkylation of carbon acids have been disclosed by the Merck process group.[28] The first example is the dialkylation of a glycine imine ester with 1,3-dibromobutene to give an enantioenriched cyclopropane-containing product (Scheme 4, eq 2).[28a] Despite a broad survey of different *Cinchona*-derived catalysts, the best enantioselectivity observed is 89:11 er. The same group recently reported the use of bis-quaternary ammonium salts as especially efficient phase-transfer catalysts for the preparation of a spiro-azaoxindole (Scheme 4, eq 3).[28b] Both the yield and enantioselectivity are significantly improved by changing to the diquaternized catalyst, and the catalyst loading could be reduced to 0.3 mol % while still providing excellent enantioselectivity (97:3 er).

2.3. Objectives. The primary objective of this study is to develop a catalytic, enantioselective [2,3]-Wittig rearrangement. The application of phase-transfer catalysis to sigmatropic rearrangements remains largely unexplored, and the use of chiral catalysts is unknown. Most examples of asymmetric phase-transfer catalysis for creating carbon−carbon bonds involves the bimolecular reactions of enolates,[29] and this mode of catalysis may be applicable to sigmatropic rearrangements that proceed through intramolecular reactions of an enolate anion. On the basis of this hypothesis the following goals were set for this investigation: (1) identify an allyloxy carbonyl compound that undergoes selective [2,3]-Wittig rearrangement under PTC conditions, (2) test if the rearrangement is dependent upon phase transfer agent (i.e., is catalysis possible), and (3) test chiral nonracemic quaternary

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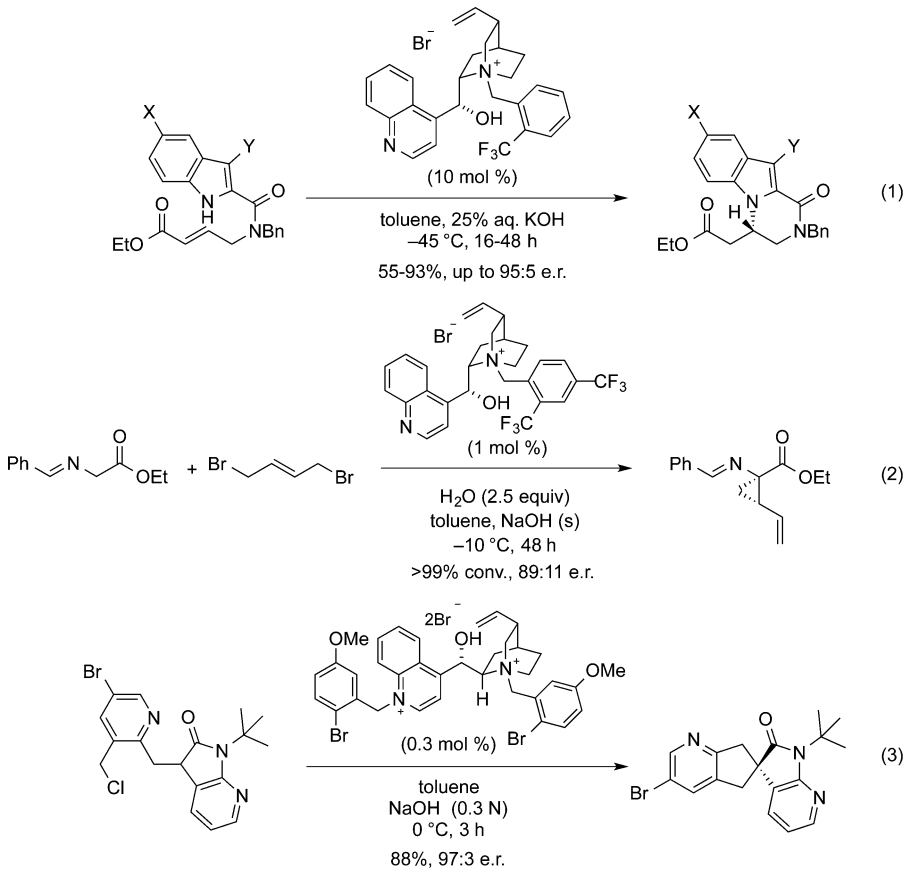
Scheme 4



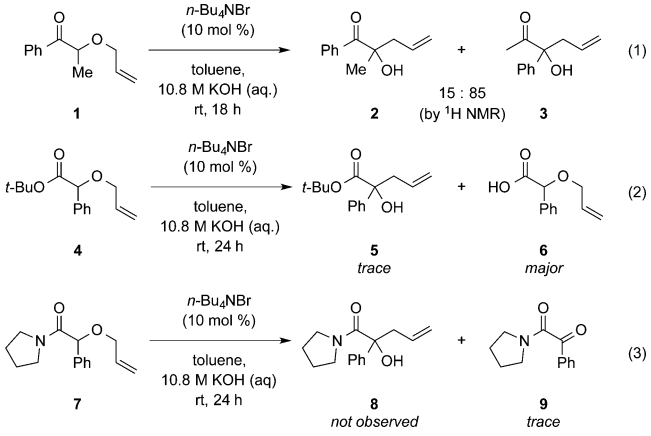
ammonium salts as phase transfer catalysts toward the development of an enantioselective method.

3. RESULTS

3.1. Substrate Identification. To address the first objective of finding a suitable substrate for the proposed [2,3]-rearrangement, a variety of allyloxy-substituted carbonyl compounds were prepared and tested. Initial studies focused on acyclic allyloxy carbonyl derivatives. Depending upon substitution patterns and reaction conditions, both [2,3]- and [3,3]-rearrangement have been reported for this class of compounds.[30] It was unclear what the outcome would be under phase-transfer conditions. α-Substituted allyloxy carbonyl substrates bearing benzoyl, *tert*-butoxycarbonyl, and pyrrolindocarbonyl functional groups were targeted for initial testing. Preparation of these substrates was nontrivial because of their base lability and tendency to undergo rearrangement. Allyloxy ketone substrate **1** was prepared by Lewis acid catalyzed OH-insertion of allyl alcohol into the corresponding α-diazo ketone as reported by Salomon.[31] Allyloxy ester substrate **4** was prepared by allylation under neutral conditions by activation with Ag_2O.[32] Allyloxy amide substrate **7** was prepared by direct allylation of the α-hydroxy amide using sodium hydride/allyl bromide.[33]

Initial testing of acyclic allyloxy-carbonyl derivatives under phase-transfer conditions was not promising. Allyloxy ketone **1** underwent rearrangement using liquid–liquid PTC conditions to give two products, phenyl ketone **2** resulting from [2,3]-rearrangement and methyl ketone **3** resulting from [3,3]-rearrangement in a ratio of 15:85 as determined by ^{1}H NMR integration (Scheme 5, eq 1). Changes in reaction conditions did not significantly impact this ratio, and due to difficulties in

Scheme 5



analyzing an inseparable mixture, this substrate was not investigated further. Exposure of allyloxy ester **4** to the same conditions afforded the [2,3]-rearrangement product **5** in only trace amounts, and the mass recovery of these reactions was poor (50–70%). Upon acidification of the aqueous extract, it was discovered that the *tert*-butyl ester underwent hydrolysis to carboxylic acid **6** under the reaction conditions. Typically, *tert*-butyl esters are not base labile, but this substrate might hydrolyze via ketene formation.[34] Allyloxy amide **7** failed to

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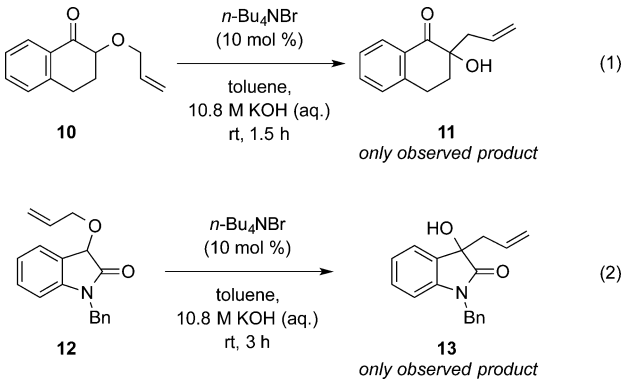
rearrange under phase-transfer conditions, and the only observed product, **9**, arose from oxidative degradation.[35]

The intervention of alternative reaction pathways when testing acyclic allyloxycarbonyl substrates suggested that restricting conformations of the starting enolate within a cyclic system might favor productive [2,3]-rearrangement. Indeed, 2-(allyloxy)-1-tetralone undergoes selective [2,3]-rearrangement by Lewis base activation of the corresponding silyl enol ether, and the ratio of competitive [3,3]-rearrangement is dependent on the counterion.[36] This report directly contrasts a report of selective [3,3]-rearrangement of 2-(allyloxy)-1-tetralone using a Rh catalyst.[37] Accordingly, 2-(allyloxy)-1-tetralone was prepared by Lewis-acid catalyzed OH-insertion from the diazo ketone. Additionally, 3-(allyloxy)-2-oxindoles were also targeted as potential cyclic substrates. In the case of allyloxy amides, exclusive [2,3]-rearrangement was anticipated because of the thermodynamic disadvantage of disrupting the amide bond in a [3,3]-rearrangement. Upon subjecting 2-(allyloxy)-1-tetralone (**10**) to liquid–liquid PTC conditions, only the [2,3]-rearrangement to 2-hydroxy-2-allyl-1-tetralone (**11**) was observed with no observable [3,3]-rearrangement product (Scheme 6, eq 1). Similarly, 3-(allyloxy)-2-oxindole (**12**) also underwent clean conversion to the desired [2,3] rearrangement product **13** (Scheme 6, eq 2). Both of these cyclic allyloxycarbonyl derivatives were chosen for further optimization.

Scheme 6

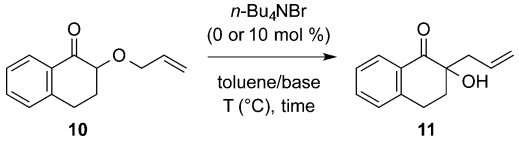


3.2. Reaction Optimization and Background Conversion. To develop a phase-transfer catalyzed [2,3]-rearrangement, initial investigations focused on evaluating reactivity under a variety of PTC conditions. Of particular importance was the question of background rates. For this process to be enantioselective, the [2,3]-rearrangement must be dependent upon the quaternary ammonium salt. The rate of rearrangement of the intermediate enolate when associated with the catalyst must be faster than the rate of rearrangement in the absence of catalyst.

Hydroxide-initiated PTC reactions of enolate ions are believed to proceed through an interfacial mechanism.[38] In this mechanism, deprotonation of the carbon acid occurs at the interfacial region between the organic and aqueous layers. The deprotonation event occurs without a quaternary ammonium salt, and it is thought that the role of the catalyst is to transport the reactive anion into the organic phase where it can react with an organic soluble electrophile. At the outset of this investigation it was unclear if deprotonation would be sufficient to cause rearrangement without the aid of a phase transfer agent. For this reason, optimization studies included testing all conditions in the absence of catalyst to estimate the background rate of conversion and whether catalysis was achieved.

The results of testing different PTC conditions for the rearrangement of 2-(allyloxy)-1-tetralone (**10**) are summarized in Table 1. Both solid–liquid and liquid–liquid PTC conditions led to exclusive formation of the desired [2,3]-rearrangement product. Full conversion of the starting material was observed very quickly in the case of solid–liquid PTC; however, the rearrangement did not require the quaternary ammonium salt (entries 1–6). Liquid–liquid PTC conditions using 10.8 M aq KOH did require a phase-transfer agent. Full conversion was observed at rt in 1.5 h using 10 mol % of *n*-Bu_4NBr (entry 7), whereas unreacted starting material was recovered in the absence of ammonium salt (entry 8). Performing the reaction at lower temperature (3–5 °C) increased the time needed for full conversion to 6 h (entry 9). The background rates were modest at extended reaction times (entries 10–11). Changing the base used to 50 wt % aq NaOH (18.9 M aq NaOH) greatly increased the background rate (entry 12).

Table 1. Phase-Transfer-Catalyzed Rearrangement of 2-(Allyloxy)-1-Tetralone[a]



entry	cat. loading (mol %)	base	temp (°C)	time (h)	rel conv[b] (%)
1	10	KOH (s)	23	1.5	100
2	none	KOH (s)	23	1.5	100
3	10	NaOH (s)	23	1.5	100
4	none	NaOH (s)	23	1.5	100
5	10	$CsOH·H_2O$ (s)	23	1.5	100
6	none	$CsOH·H_2O$ (s)	23	1.5	100
7	10	10.8 M aq KOH	23	1.5	100
8	none	10.8 M aq KOH	23	1.5	0[c]
9	10	10.8 M aq KOH	3–5	6	100
10	none	10.8 M aq KOH	3–5	24	11
11	none	10.8 M aq KOH	3–5	42	19
12	none	18.9 M aq NaOH	3–5	6	75

[a]Reactions performed on a 0.12 mmol scale. [b]Determined by ^1H NMR spectroscopic analysis on the crude reaction mixture by relative integration using a long delay (d1 = 15 s). [c]Within the limits of detection.

The results of testing different PTC conditions for the rearrangement of a small subset of 3-(alkenyloxy)-2-oxindoles (**12a–c**) are summarized in Table 2. For these substrates, the concentration of base greatly influenced the background rate in the absence of catalyst. Reactions performed with 10.8 M aq KOH did not require a quaternary ammonium salt, regardless of temperature (entries 1–4). Upon decreasing the base concentration to 5 M aq KOH, the reactions did show a dependence on the phase-transfer agent; full conversion was observed in 0.5 h in the presence of 10 mol % of *n*-Bu_4NBr (entry 5), with very little conversion in the absence of quaternary ammonium salt even at extended reaction times (entries 6 and 7). Full conversion of the substrate was observed

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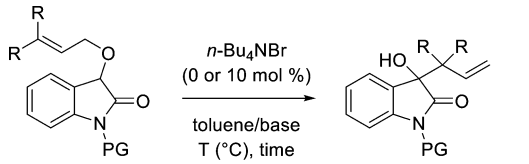
in the absence of catalyst at 24 h, however (entry 8). The time necessary for full conversion increased when base concentration was lowered to 2 M aq KOH (entry 9), and solid−liquid PTC conditions again did not show any dependence on quaternary ammonium salt (entries 11 and 12). Two additional substrates were prepared that contained additional substituents on the alkene (**12b**) or a different N-protecting group (**12c**). These substrates were also tested under the standard reaction conditions (5 M aq KOH/toluene, 3−5 °C). Dimethyl substitution at the terminus of the alkene was well tolerated and this substrate showed similar reactivity to the parent substrate **12a** (entries 13- 15). Changing the N-protecting group to isopropyl also had little impact (entries 16−18). An analogue containing a cinnamyloxy group was also prepared; however, when subjected to the standard reaction conditions, a mixture of products was obtained resulting from both [2,3]- and [1,2]-rearrangement (see the Supporting Information for more details).

Table 2. Phase-Transfer-Catalyzed Rearrangement of 3-(Allyloxy)-2-oxindoles[a]



12a = R=H, PG=Bn
12b = R=Me, PG=Bn
12c = R=Me, PG=*i*-Pr

13a = R=H, PG=Bn
13b = R=Me, PG=Bn
13c = R=Me, PG=*i*-Pr

entry	substrate	cat. loading (mol %)	base KOH (M)	temp (°C)	time (h)	rel conv[b] (%)
1	**12a**	10	10.8 (aq)	rt	3	100
2	**12a**	none	10.8 (aq)	rt	3	100
3	**12a**	10	10.8 (aq)	3−5	0.25	100
4	**12a**	none	10.8 (aq)	3−5	0.25	100
5	**12a**	10	5 (aq)	3−5	0.5	100
6	**12a**	none	5 (aq)	3−5	0.5	0[c]
7	**12a**	none	5 (aq)	3−5	4	2
8	**12a**	none	5 (aq)	3−5	24	100
9	**12a**	10	5 (aq)	3−5	8	100
10	**12a**	none	5 (aq)	3−5	8	0[c]
11	**12a**	10	solid	3−5	0.5	100
12	**12a**	none	solid	3−5	0.5	100
13	**12b**	10	5 (aq)	3−5	0.5	100
14	**12b**	none	5 (aq)	3−5	0.5	0[c]
15	**12b**	none	5 (aq)	3−5	3	4
16	**12c**	10	5 (aq)	3−5	0.5	100
17	**12c**	none	5 (aq)	3−5	0.5	0[c]
18	**12c**	none	5 (aq)	3−5	3	0[c]

[a]Reactions performed on a 0.09 mmol scale. [b]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by relative integration using a long delay (d1 = 15 s). [c]Within the limits of detection.

3.3. Testing Chiral Catalysts for the Rearrangement of 2-(Allyloxy)-1-tetralone. A variety of chiral phase-transfer catalysts were chosen to test for enantioselectivity (Figure 1). Initial studies focused on easily prepared analogues of cinchonidine (**Q1**−**Q13**) but later expanded to include the cyclopenta[*gh*]pyrrolizidinium scaffold designed in these laboratories (**Q14**−**Q15**)[39] and the spiro-binaphthyl ammonium scaffold designed by Maruoka (**Q16**).[40]

The results of phase-transfer-catalyzed [2,3]-rearrangement of **10** with these quaternary ammonium salts are collected in Table 3. To our surprise, the chiral nonracemic quaternary ammonium salts resulted in a significantly slower reaction, with incomplete conversion observed even after 42 h in some cases. Tetrabutylammonium bromide catalyzed complete conversion at 10 mol % loading after just 6 h (Table 1, entry 9). Low conversion was particularly evident with the *Cinchona*-derived catalysts bearing an unprotected hydroxyl group (entries 1−10). Although modest, the enantioselectivity observed for some of these catalysts (entry 9, 77:23) was encouraging and unprecedented. Cinchonidine derivatives bearing alkoxy groups led to lower conversion (entries 11−13), and the enantiomeric ratios were diminished. This outcome implies that the hydroxyl group is necessary for enantioselection. Cyclopenta[*gh*]-pyrrolizidinium catalysts **Q14** and **Q15** produced near-racemic product; however, good levels of conversion were observed for catalyst **Q15** which bears a very lipophilic *n*-hexyl substituent. Spiro-binaphthyl ammonium catalyst **Q16** also showed better levels of conversion in only 6 h. Unfortunately, the desired product was obtained as a racemic mixture.

Initial screening showed that promising enantioselectivity could be obtained using cinchonidine-derived catalysts, but conversion was problematic. This behavior was particularly concerning since the reactivity of **10** in the *absence* of catalyst (Table 3, entries 19 and 20) was similar to the conversion in the presence of these catalysts (Table 3, entry 3). The fact that enantioenrichment was still observed for these reactions implies that the measurement of conversion in the absence of catalyst may not be representative of the racemic background rate occurring in the presence of quaternary ammonium salt. Clearly, the kinetics of the reaction and the changes within the interfacial region are more complicated than originally assumed. Increasing the catalyst loading of **Q10** to 20 and 40 mol % (Table 3, entries 17 and 18) resulted in even lower conversion, implying a lack of catalyst turnover. Preliminary investigations indicate that product inhibition may be operative (see the Supporting Information for more details). As it was unlikely that this issue could be overcome easily, further investigation was focused on alternative substrates.

3.4. Testing of Chiral Catalysts for the Rearrangement of 3-(Alkenyloxy)-2-oxindoles. A similar survey of enantiopure, quaternary ammonium salts was performed for the [2,3]-rearrangement of **12a** (Table 4). Unlike the previous substrate, full conversion was observed for most catalysts after 4 h. This rate was somewhat slower than was observed using tetrabutylammonium bromide, which showed full conversion in 0.5 h (Table 2, entry 5); however, it was well within the range of the minimal conversion observed in the absence of catalyst (Table 4, entry 14). Unfortunately, the observed enantiomeric ratios were modest for a variety of *N*-alkylated cinchonidine-derived catalysts (entries 1−10). Cinchonidine-derived catalysts with *O*-alkyl groups (**Q12** and **Q16**) showed a slight preference for the opposite enantiomer (entries 12 and 13), but the selectivity was still poor. Although the initial enantiomeric ratios were less promising for the 3-(allyloxy)-2-oxindole substrate, conversion was significantly higher.

The low observed enantioselectivity upon initial screening was perhaps not all that surprising when one considers the enantiodetermining event being tied to differentiating conformations of a single allyl group within the substrate. It was hypothesized that changes in the substrate architecture could allow the catalyst to better discriminate between these

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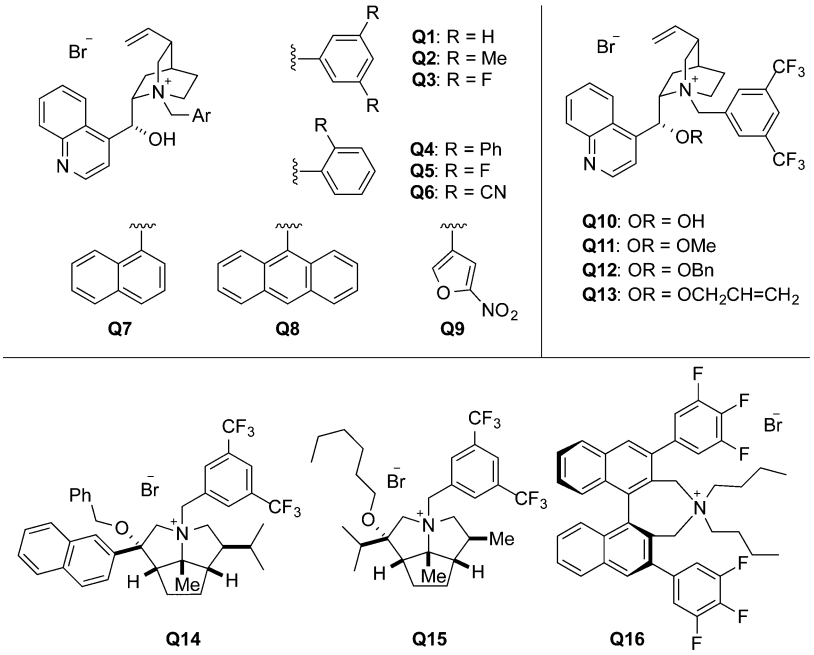
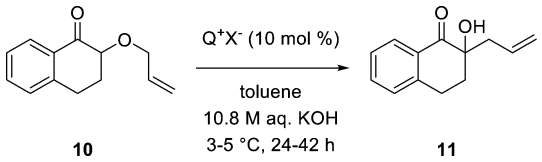


Figure 1. Chiral nonracemic quaternary ammonium phase-transfer catalysts tested in the phase-transfer-catalyzed [2,3]-rearrangement.

Table 3. Survey of Chiral Quaternary Ammonium Phase-Transfer Catalysts for [2,3]-Rearrangement of 2-(Allyloxy)-1-tetralone

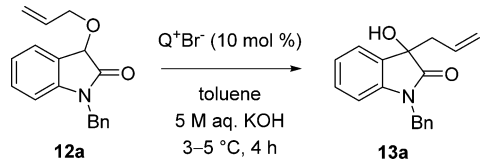


10 11

entry	catalyst (Q^+X^-)	time (h)	rel conv[b] (%)	er[c]
1	**Q1**	42	32	75:25
2	**Q2**	24	82	57:43
3	**Q3**	24	14	63:37
4	**Q4**	24	34	64:36
5	**Q5**	24	46	56:44
6	**Q6**	24	36	63:37
7	**Q7**	42	65	73:27
8	**Q8**	42	50	72:28
9	**Q9**	24	47	77:23
10	**Q10**	42	32	75:25
11	**Q11**	42	48	54:46
12	**Q12**	42	52	49:51
13	**Q13**	42	44	52:48
14	**Q14**	24	22	54:46
15	**Q15**	24	76	51:49
16	**Q16**	6	58	52:48
17[d]	**Q10**	24	25	nd
18[e]	**Q10**	24	23	nd
19[f]	none	24	11	–
20[f]	none	42	19	–

[a]Reactions performed on a 0.12 mmol scale and employed 0.10 equiv of PTC catalyst **Q1**–**Q10** and 22.0 equiv of aq KOH (0.16 M) in toluene at 3–5 °C. [b]Determined by integration of ^{1}H NMR spectrum of the crude reaction mixture. [c]Determined by CSP–SFC analysis of the crude reaction mixture. [d]Performed with 20 mol % of catalyst. [e]Performed with 40 mol % of catalyst. [f]Reaction performed in the absence of catalyst.

Table 4. Survey of Chiral Quaternary Ammonium Phase-Transfer Catalysts for [2,3]-Rearrangement of 3-(Allyloxy)-1-benzyl-2-oxindole



12a 13a

entry	catalyst (Q^+X^-)	conv[b] (%)	er[c]
1	**Q1**	100	60:40
2	**Q2**	56	65:35
3	**Q3**	65	65:35
4	**Q4**	81	57:32
5	**Q5**	100	63:37
6	**Q6**	85	54:46
7	**Q7**	78	54:46
8	**Q8**	100	61:39
9	**Q9**	38	61:39
10	**Q10**	98	53:47
11	**Q11**	100	54:46
12	**Q12**	97	36:64
13	**Q16**	88	42:58
14[d]	none	2	–

[a]Reactions performed on a 0.09 mmol scale with 10.0 equiv of KOH (0.16 M) in toluene. [b]Determined by crude ^{1}H NMR integration relative to hexamethyldisilane as an internal standard. [c]Determined by CSP–SFC. [d]Reactions performed in the absence of catalyst.

diastereomeric transition states. To test this hypothesis, substrates with both a larger alkenyl group (**12b**) and a larger nitrogen protecting group (**12c**) were investigated (Table 5). Although these substrates did react with similar rates compared to **12a**, no discernible increase in enantioselectivity was observed. A variety of differentially *N*-alkylated cinchonidine catalysts were tested; unfortunately, the highest enantiomeric ratio observed was 73:27 (Table 5, entry 9). Even catalysts bearing nontraditional heterocyclic functional groups, such as

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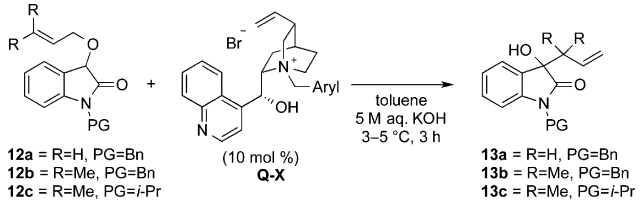
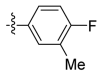
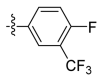
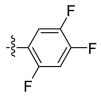
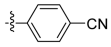
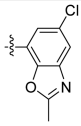
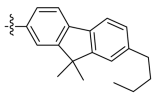
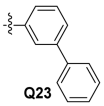
Table 5. Short Survey of Different 3-(Alkenyloxy)-1-protected-2-oxindoles in the Phase-Transfer-Catalyzed [2,3]-Rearrangement



12a = R=H, PG=Bn
12b = R=Me, PG=Bn
12c = R=Me, PG=*i*-Pr

(10 mol %)
Q-X

13a = R=H, PG=Bn
13b = R=Me, PG=Bn
13c = R=Me, PG=*i*-Pr

entry	substrate	R	Pg	catalyst **x** (Aryl=)	conversion (%)[b]	e.r.[c]
1	**12a**	H	Bn		100	69:32
2	**12b**	Me	Bn		92	62:38
3	**12c**	Me	*i*-Pr	**Q17**	100	70:30
4	**12a**	H	Bn		100	62:38
5	**12b**	Me	Bn		100	53:47
6	**12c**	Me	*i*-Pr	**Q18**	100	68:32
7	**12a**	H	Bn		90	64:36
8	**12b**	Me	Bn		100	61:39
9	**12c**	Me	*i*-Pr	**Q19**	100	73:27
10	**12a**	H	Bn		87	60:40
11	**12b**	Me	Bn		97	55:45
12	**12c**	Me	*i*-Pr	**Q20**	n.d.[d]	71:29
13	**12a**	H	Bn		100	67:33
14	**12b**	Me	Bn		100	54:46
15	**12c**	Me	*i*-Pr	**Q21**	100	61:39
19	**12a**	H	Bn		100	69:31
20	**12b**	Me	Bn		100	62:38
21	**12c**	Me	*i*-Pr	**Q22**	100	63:37
22	**12a**	H	Bn		100	68:32
23	**12b**	Me	Bn		100	65:35
24	**12c**	Me	*i*-Pr	**Q23**	100	65:35
25	**12a**	H	Bn	*none*	2[f]	-
26	**12b**	Me	Bn	*none*	4	-
27	**12c**	Me	*i*-Pr	*none*	0[g]	-

[a]Reactions performed on a 0.09 mmol scale with 10.0 equiv of KOH (0.16 M) in toluene. [b]Determined by crude ^{1}H NMR ($CDCl_3$). [c]Determined by CSP–HPLC. [d]Indicates incomplete conversion as indicated by TLC. [e]Estimated conversion due to complex mixture of side products. [f]Measured at 4 h. [g]Within the detection limits of ^{1}H NMR.

Q21 (entries 13–15), and extended π-surfaces, such as **Q22** and **Q23** (entries 19–24), had little impact.

Considering the results in Tables 4 and 5, it appears that the *N*-alkyl group on the cinchonidine has little influence on the observed enantioselectivity. This outcome may imply that the substrate is bound to the catalyst in an area that is remote to this cationic region. Interaction between the substrate and catalyst may also change significantly with the recently reported diquaternized *Cinchona* analogues.[28] A variety of diquaternized cinchonidine analogues were prepared to test the affect of dicationic catalysts on the observed enantioselectivity in the [2,3]-rearrangement of **12b** (Figure 2). The monoquaternized analogues were tested as well for the purpose of comparison (Table 6).

The results of this survey are provided in Table 6. In most cases, a small increase in the enantiomeric ratio was observed when moving from a monoquaternized cinchonidine derivative to the symmetrically diquaternized catalyst. Again, it appears that substitution pattern on the aromatic group did not have a significant impact on the observed enantioselectivity, as most

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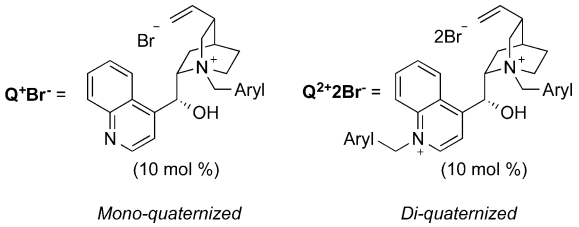


Figure 2. Chiral nonracemic quaternary ammonium phase-transfer catalysts derived by mono- and dialkylation of cinchonidine.

catalysts resulted in an modest enantiomeric ratio of approximately 70:30 er.

The only catalyst tested that provided a significantly lower level of enantioselection was catalyst **di-Q28** containing strongly electron-donating groups (Scheme 7, eq 1). Oddly, catalyst **di-Q28** was previously identified as the optimal catalyst for an intramolecular alkylation of an oxindole substrate (Scheme 4, eq 3). To test if an aromatic surface was even necessary to obtain the levels of enantioselection observed, a diallyl-quaternized cinchonidine derivative (**di-Q29**) was prepared (Scheme 7, eq 2). The observed enantiomeric ratio of 68:32 for diallyl catalyst **di-Q29** provides some evidence that an aryl group is not needed for selectivity.

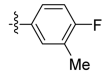
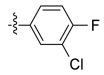
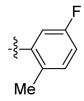
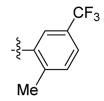
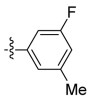
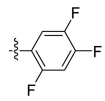
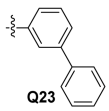
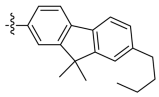
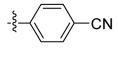
4. DISCUSSION

The results presented in the previous section demonstrate that catalysis of an anionic, [2,3]-sigmatropic rearrangement of allyloxycarbonyl compounds is possible using phase-transfer conditions. To facilitate discussion of the results, a mechanism will be proposed followed by a discussion of the nature of catalysis, reaction optimization, and stereoselection.

4.1. Proposed Mechanism for Phase-Transfer Catalysis of [2,3]-Sigmatropic Rearrangements. The hydroxide-mediated, phase-transfer-catalyzed, [2,3]-Wittig rearrangement most likely proceeds through an interfacial mechanism, often invoked for other PTC processes using hydroxide base.[38,41] A proposed mechanism that operates under liquid−liquid PTC conditions is provided in Figure 3. Following the mechanistic proposal for enolate alkylations, it is believed that the first step is diffusion of the neutral substrate into the interfacial region (a water-rich organic phase at the boundary of two immiscible layers) (step 1). Once in the interfacial region, the substrate can undergo deprotonation with inorganic base (MOH) to form a metal enolate (step 2). After formation of the metal enolate, two pathways are possible. The metal enolate could undergo rearrangement directly within the interfacial region, resulting in the formation of a metal alkoxide (step 3a). This process would be independent of the quaternary ammonium salt (Q^+Br^-) and even if an enantiomerically enriched catalyst were used, this pathway would afford a racemic product.

Alternatively, the metal enolate could undergo ion exchange with the quaternary ammonium salt at the interface to give an ammonium enolate (step 3b). This exchange process is crucial to observe high enantioselectivity with chiral, enantiomerically enriched quaternary ammonium salts. Rearrangement of the ammonium enolate should be highly dependent upon the solvation state (and therefore the reactivity) of the anion, and it is possible that rearrangement could occur in two different locations. Exchange to the ammonium counterion could provide sufficient activation to promote rearrangement within the interfacial region, resulting in the formation of an ammonium alkoxide (step 4a). Alternatively, extraction of the ammonium enolate into the organic layer may be necessary to promote rearrangement (step 4b). This extraction would likely be accompanied by desolvation of the enolate anion.

Table 6. Survey of Monoquaternized and Diquaternized *Cinchona*-Derived Phase-Transfer Catalysts for [2,3]-Rearrangement of 3-(Allyloxy)-1-benzyl-2-oxindole

entry	catalyst (Ar)	Q^+Br^- e.r.[b]	$Q^{2+}2Br^-$ e.r.[b]
1	 Q17	62:38	70:30
2	 Q24	62:38	69:31
3	 Q25	55:45	69:31
4	 Q26	48:52	69:31
5	 Q27	60:40	74:26
6	 Q19	61:39	68:32
7	 Q23	65:35	70:30
8	 Q5	59:41	68:32
9	 Q22	62:38	68:32
10	 Q20	55:45	66:34

[a]Reactions performed on a 0.09 mmol scale with 10 equiv of KOH (0.16 M) in toluene. [b]Determined by CSP−HPLC.

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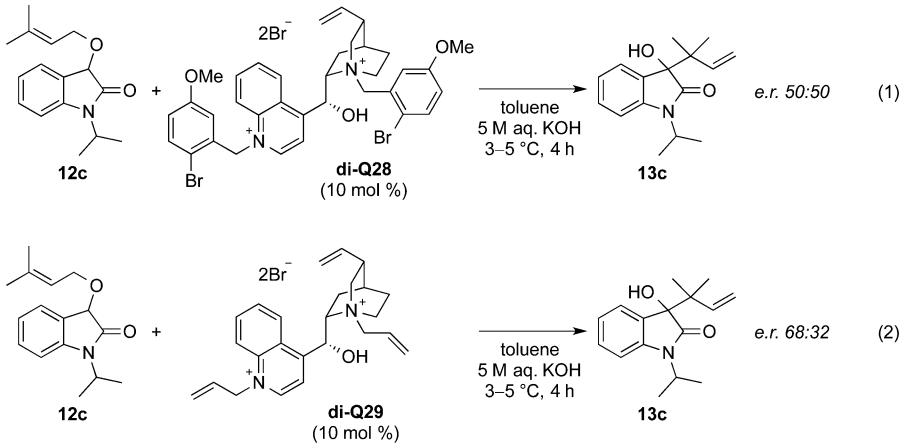
Scheme 7



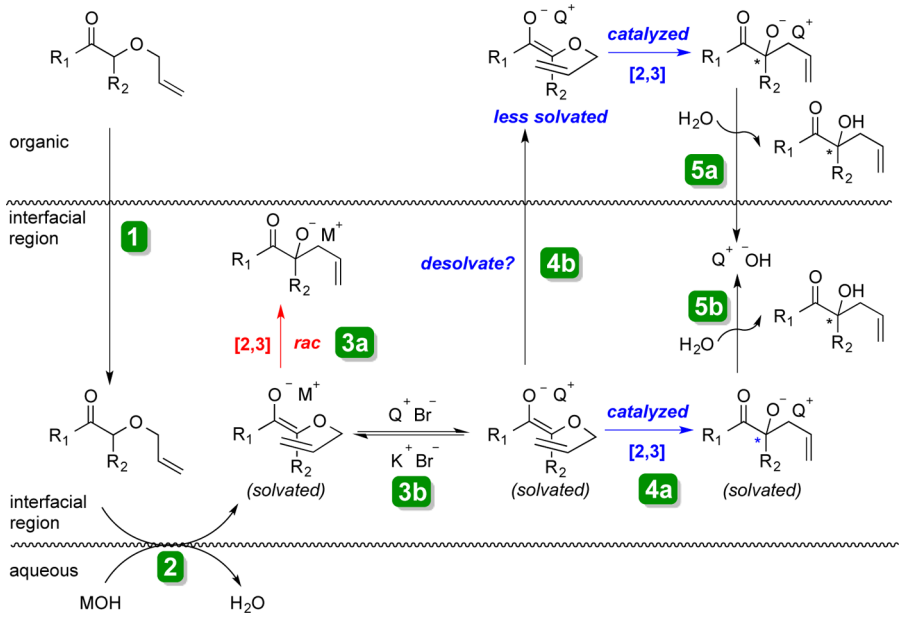


Figure 3. Proposed interfacial mechanism for a phase-transfer-catalyzed [2,3]-rearrangement.

The last step of this process is to regenerate a catalytically competent species. The alkoxide ion pair must release the quaternary ammonium counterion for the catalytic cycle to continue. One possible release mechanism is the protonation of the ammonium alkoxide by a water molecule to give the α-hydroxycarbonyl compound and quaternary ammonium hydroxide salt (steps 5a and 5b). Water molecules are likely in abundant supply within the interfacial region (step 5b); however, the presence of water in a nonpolar organic solvent such as toluene is much less likely (step 5a). Alternative release mechanisms (step 5a) to regenerate the catalyst include: (1) deprotonation of the substrate by the ammonium alkoxide within the organic layer or (2) migration of the ammonium alkoxide to the interfacial region prior to protonation. Additionally, protonation may not be necessary and exchange to a metal alkoxide could also occur by reaction with the inorganic base within the interfacial region (not shown for simplicity). The fact that a sigmatropic rearrangement is a unimolecular reaction introduces a level of complexity not found in bimolecular reactions as this release mechanism is key for catalytic turnover.

4.2. Origin of Catalysis and the Role of the Quaternary Ammonium Halide Salt. In bimolecular phase-transfer-catalyzed reactions, the nature of catalysis by the quaternary ammonium salt is often ascribed to the extraction of the quaternary ammonium anion pair into the organic phase. This extraction process is crucial in bimolecular reactions because the neutral (often lipophilic) electrophile is located within the organic phase (and is in low local concentration within the interface). Without the quaternary ammonium ion, the metal anion is insufficiently soluble within the organic phase and, consequently, does not come into proximity of the electrophile. This spatial separation of nucleophile and electrophile serves to minimize the background (or uncatalyzed) reaction.

This scenario is clearly not applicable for *intramolecular* phase-transfer-catalyzed reactions. Thus, without spatial separation of the reacting components in separate phases, what is the nature of catalysis? On the basis of the results presented herein, and other examples of intramolecular PTC reactions,[27,28] the rate of reaction does appear to be enhanced by use of a quaternary ammonium salt. Moreover, the observation

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of enantioenrichment when chiral nonracemic catalysts are used also indicates intimate involvement of the quaternary ammonium counterion.

One factor that has been suggested to contribute to catalysis is difference in Coulombic stabilization provided by a quaternary ammonium counterion compared to a metal counterion. Metalloenolates are covalent species that possess varying degrees of ionic character in the M−O bond. As the ionic character increases (e.g., Li < Na < K < Rb < Cs), the rate of reactions of enolates (or simple alkoxides) increases.[42] The transition to quaternary ammonium ions further increases the ionic character of the interaction between the enolate oxygen and the positively charged counterion. Interestingly, strong C−H hydrogen-bonding interactions have been identified between tetraalkylammonium ions and enolates crystallographically, in solution, and computationally. Nevertheless, the effective charge on the enolate ion is considerably greater as ammonium salts compared to alkali metal salts with corresponding consequences on the rate of reactions.

Previous studies from these laboratories have reported a 60-fold increase in the rate of alkylation of phenoxide anion in homogeneous solution when changing from potassium to tetrabutylammonium cations.[43] In the context of the Wittig rearrangement, Nakai has shown that anionic charge on the α-carbon is crucial to effect [2,3]-rearrangements of allyloxy esters at low temperature.[44] Thus, the lesser anionic character of metalloenolates explains why the sodium enolate does not undergo rearrangement at the interface and instead undergoes exchange with the quaternary ammonium counterion which is then transported into the organic phase.

An additional component that is important to the rate enhancement observed in phase-transfer-catalyzed processes is the desolvation that occurs as a quaternary ammonium counterion extracts the enolate away from the interfacial region.[43,45] Enolate solvation by water in the interfacial region results in lower reactivity and slower rates of rearrangement. The role of water is evident in the observation that the allyloxy carbonyl compounds in this study undergo rapid rearrangement under anhydrous conditions (solid−liquid PTC) even in the absence of a quaternary ammonium catalyst. Similarly, no catalysis was observed in the rearrangement of 3-(allyloxy)-2-oxindoles under liquid−liquid PTC conditions using higher concentrations of base (10.8 M aq KOH, see Table 2, entry 4). Together, these observations suggest that for catalysis of this rearrangement by a quaternary ammonium salt the reactive anion must be sufficiently hydrated to attenuate the background reaction.[46] It is unclear whether the ion exchange to an ammonium counterion is sufficient to promote reaction (step 4a) or if desolvation by extraction into the organic phase is necessary (step 4b). The level of solvation of the ammonium alkoxide after rearrangement will also be crucial for release of the counterion by protonation of the alkoxide. This important catalyst turnover step is dependent upon the relative pK_a values of the starting enolate and the product alkoxide, which for oxindoles **12** should be highly favorable.

Because of the complexity of the mechanism, it is difficult to say with certainty exactly which factors are most important for catalysis. Nevertheless, catalysis is observed in the [2,3]-rearrangement of 2-(allyloxy)-1-tetralone and 3-(allyloxy)-2-oxindole substrates.

4.3. Role of Substrate Lipophilicity. One of the most interesting results from this investigation is the observed differences in reactivity between 2-(allyloxy)-1-tetralone and the 3-(allyloxy)-2-oxindole substrates. In the rearrangement of 2-(allyloxy)-1-tetralone, the optimal reaction conditions required a very concentrated base solution (10.8 M aq KOH). Very low background reactivity was observed despite the high concentration of base. On the other hand, the optimized conditions for the catalyzed rearrangement of 3-(allyloxy)-2-oxindoles required more dilute base (5 M aq KOH) as the background reaction with 50 wt % aqueous KOH was too fast. This divergence may reflect the differences in lipophilicity between the two substrate classes. Perhaps the more polar 2-oxindole substrate has a higher affinity for the water-rich interfacial region, and at higher KOH concentrations, insufficient water is present to solvate the anion and slow the rearrangement of the potassium salt.

Lipophilicity differences between the substrates may also explain the product inhibition observed for the 2-allyloxytetralone system when using phase-transfer catalysts derived from cinchonidine. It is possible that with a more lipophilic substrate the resultant ammonium alkoxide−ion pair of the product is too soluble within the organic phase, preventing protonation and release of the catalyst back into the interfacial region. When applying phase-transfer catalysis to unimolecular reactions, it may be important to consider how the structure of the substrate could impact the equilibrium exchanges at play.

4.4. Enantioselection. To date, only modest enantioselectivity has been observed in the initial testing of chiral, nonracemic quaternary ammonium bromide catalysts. This is not terribly surprising since the differences in the diastereomeric transition states leading to either enantiomer are merely changes in the conformation of the allyloxy group, and thus, stereodifferentiation would be difficult. The highest levels of enantioselectivity in the rearrangement of 3-alkenyloxy-2-oxindoles were observed using diquaternary ammonium salts derived from cinchonidine. Interestingly, varying the aryl substituents on benzyl group attached to the quinuclidinium nitrogen had very little impact on the observed enantioselectivity (er 70:30).[47] This outcome may indicate that the region in which the anion is associated with the catalyst is remote from the areas of diversification.

5. CONCLUSIONS AND OUTLOOK

In summary, two classes of cyclic (allyloxy)carbonyl compounds undergo selective [2,3]-sigmatropic rearrangement under PTC conditions. Depending upon the conditions applied, the [2,3]-sigmatropic rearrangement is dependent upon the use of a phase-transfer agent, providing a rare example of phase-transfer catalysis in intramolecular reactions. The results presented herein provide the proof of concept for a new strategy to catalyze sigmatropic rearrangements by utilizing a phase-transfer process. Initial results show modest levels of enantioselectivity with chiral nonracemic quaternary ammonium salts. Ongoing investigations are focused on obtaining a better understanding of the mechanism operative for these reactions and the identification of a catalyst scaffold that will lead to higher levels of enantioselectivity.

6. EXPERIMENTAL SECTION

6.1. General Procedure for Phase-Transfer-Catalyzed [2,3]-Rearrangement of Acyclic Allyloxy Carbonyl Substrates. To a 1-dram glass vial equipped with a plastic screw cap, Teflon septum, and 1.5 cm × 0.5 cm football-shaped stir bar were added allyloxy carbonyl substrate (0.10 mmol, 1.0 equiv), tetrabutylammonium bromide (3.3 mg, 0.010 mmol, 10 mol %), and toluene (0.40 mL, 0.26

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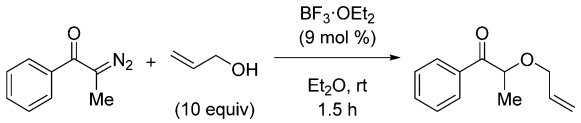
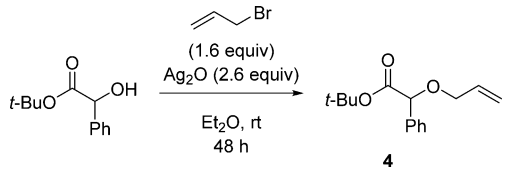
M). To this solution was added 10.8 M aq KOH (0.20 mL, 21.6 equiv) by syringe, and the reaction was stirred rapidly (1600 rpm) at rt for 18−24 h. After the reaction was complete, the reaction was diluted by the addition of distilled water (0.3 mL) and EtOAc (0.5 mL), the organic layer was removed by syringe, and the aqueous layer was extracted with EtOAc (2 × 1.0 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation to yield the crude material which was subjected to ^{1}H NMR analysis. ^{1}H NMR spectroscopic data for the observed reaction products matched the previously reported data for **2**,[48] **3**,[49] **6**,[50] and **9**.[51]

6.2. Preparation of Rearrangement Substrates.



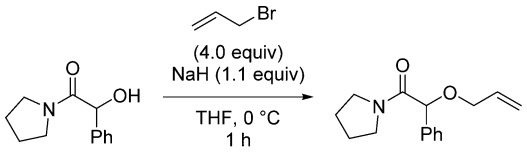
1

*Preparation of 2-(Allyloxy)-1-phenylpropan-1-one (**1**).* To a flame-dried, 50-mL, round-bottomed flask fitted with a magnetic stir bar and Ar inlet were added 2-diazopropiophenone[52] (430 mg, 2.68 mmol, 1.0 equiv) and diethyl ether (9.8 mL) to give a homogeneous, bright yellow solution. The reaction was stirred at rt, and then allyl alcohol (1.83 mL, 26.9 mmol, 10.0 equiv) and BF_3·OEt_2 (30 μL, 0.24 mmol, 9 mol %) were added by syringe in succession. Immediate gas evolution is evident upon addition of the Lewis acid. The reaction was stirred at rt for 1.5 h and then quenched by pouring into 20 mL of distilled water. This mixture was transferred to a 125-mL separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layer was washed with distilled water (1 × 20 mL) and saturated brine solution (2 × 20 mL), dried over $MgSO_4$, and concentrated by rotary evaporation to give the crude product as a yellow oil. Purification by flash chromatography (SiO_2, 170 mm × 25 mm, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution (start 100% hexanes and increase to 20% CH_2Cl_2)) yielded 2-(allyloxy)-1-phenylpropan-1-one as a colorless oil (210 mg, 41%). The ^{1}H NMR spectroscopic data matched that from an alternative preparation.[53] Data for **1**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.07−8.03 (m, 2 H), 7.61−7.54 (m, 1 H), 7.49−7.43 (m, 2 H), 5.91 (ddt, *J* = 5.7, 10.3, 17.3 Hz, 1 H), 5.27 (dq, *J* = 1.6, 17.2 Hz, 1 H), 5.18 (dd, *J* = 1.6, 10.4 Hz, 1 H), 4.76 (q, *J* = 6.9 Hz, 1 H), 4.10 (ddt, *J* = 1.5, 5.5, 12.6 Hz, 1 H), 3.95 (ddt, *J* = 1.3, 6.0, 12.5 Hz, 1 H), 1.51 (d, *J* = 6.9 Hz, 3 H); TLC R_f 0.45 (silica gel, 4:1 hexanes/EtOAc) [UV, CAM].



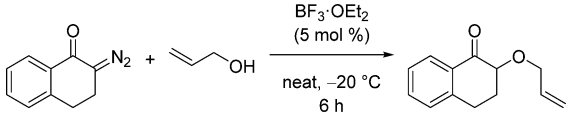
4

*Preparation of tert-Butyl 2-(Allyloxy)-2-phenylacetate (**4**).* To a flame-dried, 100-mL, single-neck, round-bottomed flask fitted with a magnetic stir bar, reflux condenser, and Ar inlet was added *tert*-butyl 2-hydroxy-2-phenylacetate[54] (851 mg, 4.09 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar twice, and then diethyl ether (16.4 mL) was added to give a cloudy white solution. The reaction was stirred at room temperature, and then allyl bromide (0.57 mL, 6.54 mmol, 1.6 equiv) and silver(I) oxide (2.46 g, 10.63 mmol, 2.6 equiv) were added successively. The flask was covered with aluminum foil and heated to reflux for 2 h. Heating was stopped, and the reaction was then stirred at rt for 48 h. The crude reaction mixture was then filtered through a short SiO_2 plug to remove silver salts and washed with a large excess of diethyl ether. The filtrate was then concentrated by rotary evaporation to yield the crude material as a colorless oil (902 mg) which was obtained as a mixture of desired product, recovered starting material, and additional oxidative side products. Purification by flash chromatography (SiO_2, 160 mm × 25 mm, 10 mL fractions, dry load on Celite, hexanes/TBME gradient 20:1 (200 mL) to 10:1 (200 mL) to 4:1 (500 mL)) yielded *tert*-butyl 2-(allyloxy)-2-phenylacetate as a colorless oil (229 mg, 23%). The ^{1}H NMR spectroscopic data was similar to the data reported for the corresponding methyl ester.[55] Data for **4**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.46−7.42 (m, 2 H), 7.38−7.30 (m, 3 H), 5.95 (ddt, *J* = 5.7, 10.3, 17.3 Hz, 1 H), 5.29 (dd, *J* = 1.6, 17.2 Hz, 1 H), 5.21 (dd, *J* = 1.7, 10.3 Hz, 1 H), 4.80 (s, 1 H), 4.11−4.00 (m, 2 H), 1.39 (s, 9 H); TLC R_f 0.38 (silica gel, 9:1 hexanes/EtOAc) [UV, I_2, $KMnO_4$].



7

*Preparation of 2-(Allyloxy)-2-phenyl-1-(pyrrolidin-1-yl)ethan-1-one (**7**).* To a flame-dried, 20-mL Schlenk flask fitted with magnetic stir bar and septum was added washed sodium hydride (23.0 mg, 0.96 mmol, 1.1 equiv). The flask was evacuated and backfilled with Ar twice, and then THF (3.0 mL) was added to give a gray-white suspension. The reaction mixture was stirred and cooled to 0 °C (ice−water bath) for 20 min. To a separate flame-dried, 25-mL conical flask with an Ar inlet were added 2-hydroxy-2-phenyl-1-(pyrrolidin-1-yl)ethan-1-one[56] (179 mg, 0.87 mmol, 1.0 equiv) and THF (4.5 mL) to give a homogeneous, colorless solution. The solution of α-hydroxy amide was then added to the Schlenk flask by cannula over 10 min while the reaction temperature was maintained below 5 °C. Over the course of addition, gas evolution was observed and the reaction mixture turned pale yellow. The reaction mixture was stirred at 0 °C for 1 h, and then allyl bromide (302 μL, 3.5 mmol, 4.0 equiv) was added in one portion. The reaction was stirred for an additional 1 h at 0 °C, and then the reaction was quenched by addition of distilled water (4.0 mL). The reaction mixture was transferred to a 125-mL separatory funnel with distilled water (15 mL) and ethyl acetate (30 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layer was washed with saturated brine (1 × 20 mL), dried over $MgSO_4$, and concentrated by rotary evaporation to yield crude allyloxy amide as a yellow solid (210 mg). Purification by flash chromatography (SiO_2, 160 mm × 25 mm, 10 mL fractions, CH_2Cl_2/MeOH gradient elution: 100% CH_2Cl_2 (200 mL) to 1% MeOH in CH_2Cl_2 (200 mL) to 2.5% MeOH in CH_2Cl_2 (400 mL)) yielded 2-(allyloxy)-2-phenyl-1-(pyrrolidin-1-yl)ethano-1-one as a low-melting white solid (197 mg, 92%). The ^{1}H NMR spectroscopic data matched that from an analogous compound previously reported in the literature.[57] Data for **7**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.48−7.43 (m, 2 H), 7.39−7.28 (m, 3 H), 5.97 (ddt, *J* = 5.7, 10.4, 17.5 Hz, 1 H), 5.31 (dq, *J* = 1.7, 17.3 Hz, 1 H), 5.22 (dq, *J* = 1.4, 10.4 Hz, 1 H), 5.07 (s, 1 H), 4.09 (ddt, *J* = 1.5, 5.9, 7.3 Hz, 2 H), 3.58−3.43 (m, 2 H), 3.36 (td, *J* = 2.0, 6.5 Hz, 2 H), 1.86−1.69 (m, 4 H); TLC R_f 0.30 (silica gel, 7:3 hexanes/EtOAc) [UV, I_2, $KMnO_4$].



10

*Preparation of 2-(Allyloxy)-1-tetralone (**10**).* The preparation of 2-(allyloxy)-1-tetralone followed the preparation reported by Mukaiyama with minor changes.[58] To a flame-dried, 20-mL Schlenk flask fitted with a magnetic stir bar and septum were added 2-diazo-1-tetralone[52] (938 mg, 5.45 mmol, 1.0 equiv) and allyl alcohol (7.3 mL). The reaction was cooled to −20 °C in a 20 wt % $CaCl_2$ (aq)/CO_2 (s) bath, stirred, and covered with aluminum foil. To this solution was added BF_3·OEt_2 (34 μL, 0.27 mmol, 5 mol %) at the beginning of the reaction, after 3 h, and after 5 h (15 mol % total). The reaction was then quenched after 6 h by addition of 10 mL of saturated aqueous $NaHCO_3$. The reaction mixture was transferred to a 125-mL separatory funnel and extracted with diethyl ether (3 × 30 mL). The combined organic layer was washed with distilled water (1 × 20 mL) and saturated brine solution (1 × 20 mL), dried over $MgSO_4$, and concentrated by rotary evaporation to yield the crude material as a thick brown oil. Purification by flash chromatography (SiO_2, 160 mm

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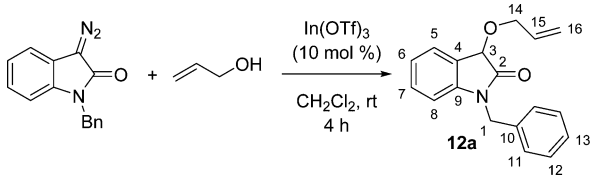
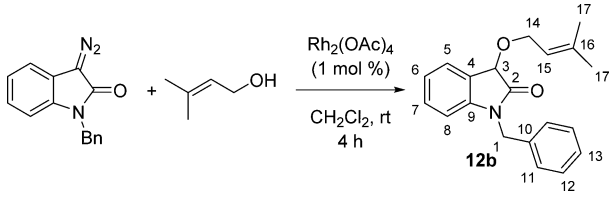
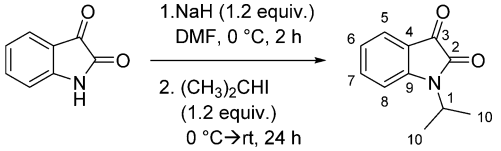
× 35 mm, 20 mL fractions, dry load on Celite, isocratic elution with 2% acetone in hexanes) yielded 2-(allyloxy)-1-tetralone as a pale yellow oil (485 mg, 44%). The ^{1}H NMR spectroscopic data matched that from an alternative preparation.[58] Data for **10**: ^{1}H NMR (400 MHz, $CDCl_3$) 8.03 (dd, J = 1.6, 7.8 Hz, 1 H), 7.48 (td, J = 1.5, 7.5 Hz, 1 H), 7.32 (t, J = 7.5 Hz, 1 H), 7.24 (d, J = 7.6 Hz, 1 H), 5.97 (ddt, J = 5.8 Hz, 10.4, 17.3 Hz, 1 H), 5.33 (dq, J = 1.7 Hz, 17.2 Hz, 1 H), 5.21 (dq, J = 1.3, 10.3 Hz, 1 H), 4.39 (ddt, J = 1.5, 5.3, 12.8 Hz, 1 H), 4.18 (ddt, J = 1.4, 6.0, 12.7 Hz, 1 H), 4.10 (dd, J = 4.3, 10.7 Hz, 1 H), 3.15 (dt, J = 5.0, 17.1 Hz, 1 H), 3.03 (ddd, J = 4.9, 10.0, 17.0 Hz, 1 H), 2.37 (dq, J = 4.8, 13.1 Hz, 1 H), 2.30−2.18 (m, 1 H); TLC R_f 0.41 (silica gel, 4:1 hexanes/TBME) [UV, I_2, $KMnO_4$].



*Preparation of 1-Benzyl-3-(allyloxy)-2-oxindolone (**12a**).* To a flame-dried, 25-mL Schlenk flask fitted with a magnetic stir bar and septum were added indium(III) triflate (56.4 mg, 0.10 mmol, 10 mol %) and dichloromethane (5.3 mL). The reaction mixture was stirred at rt to give a homogeneous, colorless solution, and allyl alcohol (0.11 mL, 2.0 mmol, 2.0 equiv) was added by syringe. To a separate flame-dried, 25-mL conical flask with an Ar inlet were added 1-benzyl-3-diazoindolin-2-one[59] (250 mg, 1.0 mmol, 1.0 equiv) and dichloromethane (3.0 mL) to give a deep red solution. The solution containing the diazo compound was taken up in a 5.0 mL gas-tight syringe and set up in a syringe pump for dropwise addition. The diazo compound was added over 3 h (1.0 mL/min) dropwise at rt, over which time the reaction turned an orange-brown color. After full addition, the reaction was stirred at rt for an additional 1 h, at which time complete consumption of the diazo compound was observed by TLC analysis (4:1 hexanes/EtOAc). The reaction was quenched at rt by the addition of saturated aqueous NH_4Cl (10 mL). The reaction mixture was transferred to a 125-mL separatory funnel with dichloromethane (20 mL) and distilled water (20 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layer was washed with distilled water (3 × 30 mL) and brine (1 × 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure (15 mmHg) and then placed under high vacuum (0.1 mmHg) at rt for 2 h to yield the crude material as a brown-orange oil (257.8 mg, 92%). Purification by flash chromatography (SiO_2, 25 mm × 160 mm, dry load on Celite, 10 mL fractions, hexanes/TBME gradient elution: 10:1 (500 mL) to 4:1 (500 mL) to 2:1 (500 mL)) yielded 1-benzyl-3-(allyloxy)-2-oxindolone as a pink solid (214.8 mg, 77%). An analytically pure sample can be obtained by recrystallization by slow diffusion from a super saturated solution in a minimum of $CHCl_3$ (1 mL) in a sealed container with pentane to yield long white needles. Data for **12a**: ^{1}H NMR ($CDCl_3$) 7.40 (d, J = 7.2 Hz, 1 H, HC(5)), 7.35−7.24 (m, 5 H, HC(11,12,13)), 7.21 (tt, J = 1.0, 7.7 Hz, 1 H, HC(7)), 7.05 (td, J = 1.1, 7.6 Hz, 1 H, HC(6)), 6.69 (d, J = 7.8 Hz, 1 H, HC(8)), 6.02 (ddt, J = 5.8, 10.4, 17.1 Hz, 1 H, HC(15)), 5.38 (dq, J = 1.6, 17.2 Hz, 1 H, H_2C(16)), 5.25 (dq, J = 1.3, 10.3 Hz, 1 H, H_2C(16)), 5.03 (s, 1 H, HC(3)), 4.91 (d, J = 15.8 Hz, 1 H, H_2C(1)), 4.84 (d, J = 15.8 Hz, 1 H, H_2C(1)), 4.42 (ddt, J = 1.5, 5.4, 12.2 Hz, 1 H, H_2C(14)), 4.33 (ddt, J = 1.5, 6.2, 12.2 Hz, 1 H, H_2C(14)); ^{13}C NMR (126 MHz, $CDCl_3$) 174.9 (O═C(2)), 143.4 (C(4)), 135.6 (C(10)), 134.2 (HC(15)), 130.0 (HC(7)), 128.9 (HC(11,12)), 127.8 (HC(13)), 127.5 (HC(11,12)), 125.5 (HC(5)), 125.3 (C(9)), 123.0 (HC(6)), 118.3 (H_2C(16)), 109.5 (HC(8)), 74.9 (HC(3)), 70.1 (H_2C(14)), 43.8 (H_2C(1)); IR (ATR-FTIR) 3063 (w), 3032 (w), 2867 (w), 1721 (m), 1609 (m), 1493 (w), 1467 (m), 1350 (m), 1172 (w), 1008 (w), 913 9w), 753 (m), 699 (m), 657 (w); LRMS (ES$^+$, TOF) 222.1 (63), 223.1 (12), 280.1 (100), 302.1 (28); HRMS (ESI, $[M + 1]^+$) calcd for $C_{18}H_{18}NO_2$ 280.1338, found 280.1343; TLC R_f 0.17 (silica gel, 10:1 hexanes/TBME) [UV]. Anal. Calcd for $C_{18}H_{17}NO_2$ (279.34): C, 77.40 H; 6.13; N, 5.01. Found: C, 77.38; H, 6.30; N, 4.99.



*Preparation of 3-[(3-Methylbut-2-en-1-yl)oxy]-1-benzyl-2-oxindolone (**12b**).* To a flame-dried, 25-mL Schlenk flask fitted with a magnetic stir bar and septum were added rhodium(II) acetate dimer (7.1 mg, 0.02 mmol, 1 mol %), dichloromethane (10.3 mL), and 3-methylbut-2-en-1-ol (0.21 mL, 2.09 mmol, 1.3 equiv) under Ar to give a blue-green homogeneous solution. To a separate flame-dried, 25-mL conical flask with an Ar inlet were added 1-benzyl-3-diazoindolin-2-one[59] (400 mg, 1.6 mmol, 1.0 equiv) and dichloromethane (3.0 mL) to give a deep red solution. The solution containing the diazo compound was taken up in a 5.0 mL gas-tight syringe and set up in a syringe pump for dropwise addition. The diazo compound was added over 4 h dropwise (0.75 mL/min) at rt, over which time the reaction mixture did not change color. After full addition, the reaction was stirred at rt for an additional 0.5 h, at which time complete consumption of the diazo compound was observed by TLC analysis (4:1 hexanes/EtOAc). The reaction was diluted with 1:1 hexanes/EtOAc (10 mL) and filtered through a silica plug to remove metal catalyst (4 cm × 4 cm), and the crude mixture was concentrated by rotary evaporation (15 mmHg) to yield the crude product as a yellow oil (910 mg). Purification by flash chromatography (SiO_2, 25 mm × 170 mm, load in eluent, 10 mL fractions, hexanes/EtOAc isocratic elution: 10:1 (500 mL)) yielded the desired compound as a yellow oil (443.4 mg, 88%). An analytical sample was obtained by distillation (air bath = 160 °C, 2.3 × 10^{-5} mm Hg) to yield a similarly thick yellow oil. Data for **12b**: bp 160 °C (air bath, 2.3 × 10^{-5} mm Hg); ^{1}H NMR (500 MHz, $CDCl_3$) 7.34 (d, J = 7.3 Hz, 1 H, HC(5)), 7.28−7.24 (m, 4 H, HC(11, 12)), 7.23−7.18 (m, 1 H, HC(13)), 7.15 (tt, J = 1.1, 7.8 Hz, 1 H, HC(7)), 6.99 (td, J = 7.6, 1.1 Hz, 1 H, HC(6)), 6.64 (d, J = 7.6 Hz, 1 H, HC(8)), 5.41 (dddt, J = 7.0, 5.6, 2.8, 1.4 Hz, 1 H, HC(15)), 4.96 (s, 1 H, HC(3)), 4.86 (d, J = 15.6 Hz, 1 H, H_2C(1)), 4.79 (d, J = 15.6 Hz, 1 H, H_2C(1)), 4.33 (dd, J = 11.0, 6.8 Hz, 1 H, H_2C(14)), 4.27 (dd, J = 11.0, 7.5 Hz, 1 H, H_2C(14)), 1.72 (s, 3 H, H_3C(17)), 1.66 (s, 3 H, H_3C(17)); ^{13}C NMR (126 MHz, $CDCl_3$) 175.2 (O═C(2)), 143.4 (C(9)), 139.2 (Me_2C(16)), 135.7 (C(10)), 129.8 (HC(7)), 128.9 (HC(7)), 127.8 (HC(11,12,13)), 127.8 (HC(11,12,13)), 127.4 (HC(11,12,13)), 125.6 (C(4)), 125.4 (HC(5)), 123.0 (HC(6)), 120.4 (HC(15)), 109.4 (HC(8)), 74.7 (HC(3)), 65.4 (H_2C(14)), 43.7 (H_2C(1)), 26.0 (H_3C(17)), 18.3 (H_3C(17)); IR (ATR-FTIR) 3059 (w), 3032 (w), 2970 (w), 2863 (w), 1712 (s), 1614 (m), 1489 (m), 1462 (m), 1355 (m), 1297 (w), 1168 (m), 1101 (w), 1079 (m), 1025 (w), 1008 (w), 753 (m), 700 (m), 548 (w); LRMS (ES$^+$, TOF) 222.1 (73), 223.1 (15), 240.1 (100), 241.1 (15), 308.2 (80), 309.2 (14); HRMS (ESI, $[M + 1]^+$) calcd for $C_{20}H_{22}NO_2$ 308.1651, found 308.1651; TLC R_f 0.12 (silica gel, 10:1 hexanes/TBME) [UV]. Anal. Calcd for $C_{20}H_{21}NO_2$ (307.39): C, 78.15; H, 6.89; N, 4.56. Found: C, 77.96; H, 6.98; N, 4.65.



Preparation of 1-Isopropylisatin. To a flame-dried, 250-mL, single necked, round-bottomed flask fitted with a magnetic stir bar, Ar inlet, and internal temperature probe was added isatin (8.00 g, 54.37 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar twice. The orange solid was dissolved in DMF (91 mL) to give a red, homogeneous solution. The reaction was cooled in an ice−water bath (I.T. < 1 °C), and then sodium hydride (60% dispersion in mineral oil, 2.61 g, 65.21 mmol, 1.2 equiv) was added portionwise over 15 min, keeping the temperature below 10 °C. The deep purple solution was stirred for an additional 2 h at 0 °C, and then 2-iodopropane (6.51 mL, 65.25 mmol, 1.2 equiv) was added by syringe.

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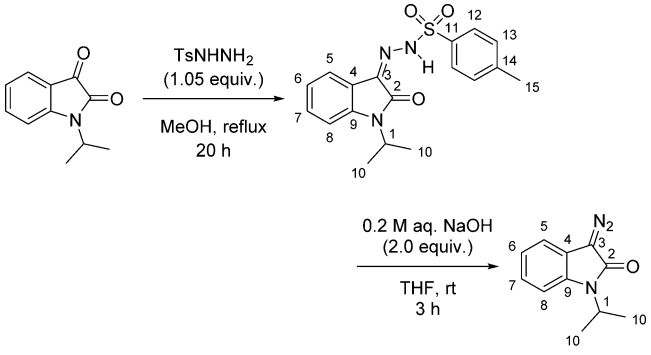
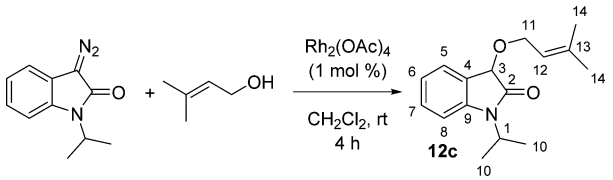
The reaction was removed from the ice bath and stirred at rt for 24 h, over which time the reaction turned a deep black-brown color. The reaction mixture was split into four portions and extracted piecewise with EtOAc (3 × 200 mL) and distilled water (200 mL) in order to avoid emulsion. The combined organics were washed with brine (1 × 150 mL), dried over Na_2SO_4, and concentrated to give a black sludge (10.47 g, > 100%). The crude material was adsorbed onto Celite and purified by silica gel column chromatography (50 mm × 140 mm, hexanes/EtOAc gradient: 20:1 (500 mL) to 15:1 (500 mL) to 10:1 (500 L) to 4:1 (2 L) to 2:1 (1 L)) to yield 1-isopropylindoline-2,3-dione as a dark orange powder (7.616 g, 74%). This material was sufficiently pure to be used directly in the next step. An analytical sample was obtained by recrystallization as follows. A portion of the isolated material (394 mg) was dissolved in a minimum of boiling 2-propanol (10 mL) to give a homogeneous, deep red solution. This solution was submitted to a hot filtration through a preheated glass funnel and Kimwipe into a 50-mL Erlenmeyer flask and diluted with an additional 15 mL of 2-propanol. The solution was reheated to homogeneity, allowed to cool to room temperature (no crystallization), and then cooled in an ice−water bath to induce crystal formation. The flask was cooled at 0 °C for 2 h and then cooled to −20 °C overnight (18 h). The shiny orange flakes were collected by Büchner filtration, allowed to dry on the filter paper for 30 min, and then collected in a scintillation vial (precleaned with No-Chromix solution). The crystals were ground using a glass stir rod then dried in a drying pistol (over P_2O_5/refluxing dichloromethane) under vacuum (0.1 mmHg) for 18 h, then at rt for 24 h. Data for 1-isopropylisatin: mp 57−58 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.61 (dd, J = 7.4, 0.7 Hz, 1 H, HC(5)), 7.56 (td, J = 7.9, 1.4 Hz, 1 H, HC(7)), 7.09 (t, J = 7.5 Hz, 1 H, HC(6)), 7.03 (dd, J = 8.1, 0.9 Hz, 1 H, HC(8)), 4.54 (hept, J = 7.0 Hz, 1 H, $(H_3C)_2HC(1)$), 1.52 (d, J = 7.0 Hz, 6 H, $H_3C(10)$); ^{13}C NMR (126 MHz, $CDCl_3$) 184.0 (O=C(3)), 158.0 (O=C(2)), 150.6 (C(4)), 138.2 (HC(7)), 125.7 (HC(6)), 123.4 (HC(5)), 118.0 (C(9)), 111.4 (HC(8)), 44.9 ($(H_3C)_2HC(1)$), 19.5 ($H_3C(10)$); IR (ATR-FTIR) 1738 (w), 1717 (w), 1598 (w), 1467 (w), 1385 (w), 1350 (w), 1300 (w), 1184 (w), 1120 (w), 1091 (w), 993 (w), 969 (w), 889 (w), 852 (w), 814 (w), 754 (w), 704 (w), 680 (w), 561 (w), 537 (w), 475 (m); HRMS (ESI, $[M + 1]^+$) calcd for $C_{11}H_{12}NO_2$ 190.0868, found 190.0871; TLC R_f 0.28 (silica gel, 4:1 hexanes/TBME) [UV].



Preparation of 3-Diazo-1-isopropylindolin-2-one. To a 250-mL, single-neck, round-bottomed flask with Ar inlet and stir bar was added 1-isopropylindoline-2,3-dione (7.18 g, 37.21 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar, and then MeOH (38.5 mL) was added. The flask was placed into a preheated oil bath (oil temperature = 60 °C) and stirred to give a homogeneous, red solution. To the hot reaction mixture was added *p*-toluenesulfonyl hydrazide (7.50 g, 39.07 mmol, 1.05 equiv) as a solid in one portion. A yellow precipitate formed within 5 min. The reaction mixture was stirred at 60 °C overnight (20 h). The oil bath was then removed, and the reaction mixture was cooled in an ice−water bath for 4 h. The yellow precipitate was isolated by vacuum filtration on a Büchner funnel and was washed with ice-cold MeOH. The free-flowing yellow powder was collected and dried under reduced pressure (0.1 mmHg) at rt for 2 h to give 12.14 g (91%) of the crude hydrazone, which was used as is in the next reaction. Data for crude hydrazone: mp 178 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) 12.53 (br s, 1 H, N−H), 7.87 (d, J = 8.3 Hz, 2 H, HC(12)), 7.48 (dd, J = 7.6, 1.2 Hz, 1 H, HC(5)), 7.44 (d, J = 8.1 Hz, 2 H, HC(13)), 7.40 (td, J = 7.5, 0.9 Hz, 1 H, HC(7)), 7.27 (d, J = 8.0 Hz, 1 H, HC(8)), 7.09 (td, J = 7.5, 0.9 Hz, 1 H, HC(6)), 4.49 (hept, J = 7.0 Hz, 1 H, $(H_3C)_2HC(1)$), 2.38 (s, 3 H, $H_3C(15)$), 1.40 (d, J = 7.0 Hz, 6 H, $H_3C(10)$); ^{13}C NMR (126 MHz, DMSO-d_6) 159.7, 144.5, 142.2, 136.5, 135.0, 129.9, 127.7, 122.7, 120.5, 119.0, 111.0, 43.7, 21.1, 19.0; IR (ATR-FTIR) 1679 (w), 1611 (w), 1466 (w), 1391 (w), 1354 (w), 1302 (w), 1207 (w), 1165 (m), 1105 (w), 1081 (w), 993 (w), 872 (w), 835 (m), 821 (w), 794 (w), 748 (m), 704 (w), 678 (w), 659 (m), 628 (m), 537 (s), 505 (w), 472 (w); HRMS (ESI, $[M + 1]^+$) calcd for $C_{18}H_{20}N_3O_3S$ 358.1225, found 358.1223; TLC R_f 0.64 (silica gel, 1:1 hexanes/EtOAc) [UV].

To a 500-mL, single-neck, round-bottomed flask fitted with stir bar, 250-mL addition funnel, and Ar inlet was added crude (*Z*)-*N*′-(1-isopropyl-2-oxoindolin-3-ylidene)-4-methylbenzenesulfonohydrazide (3.50 g, 9.79 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar. THF (40 mL) was added, and the reaction was stirred at rt to give a heterogeneous, yellow reaction mixture. The addition funnel was charged with 0.2 M aqueous NaOH solution (98 mL, 19.58 mmol, 2.0 equiv). The base solution was added at rt dropwise over 1 h and 40 min, over which time the reaction became orange and homogeneous. The reaction was then stirred at rt for an additional 3 h, at which time the reaction was complete as indicated by TLC (2:1 hexanes/EtOAc). The reaction mixture was diluted with EtOAc (100 mL) and transferred to a 500-mL separatory funnel. The aqueous layer was separated, neutralized by the addition of powdered dry ice, and then re-extracted with EtOAc (150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure (15 mmHg) to give a bright orange solid (2.22 g). The crude material was adsorbed onto Celite and purified by flash chromatography (SiO_2, 150 mm × 30 mm, dry load, 20 mL fractions, isocratic elution hexanes/EtOAc (4:1)) to yield 3-diazo-1-isopropyloxdinolin-2-one as a pale orange solid (89%). Attempts to recrystallize material from a variety of solvents were not successful. Data for 3-diazo-1-isopropylindolin-2-one: mp 113−116 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) 7.23−7.13 (m, 2 H, HC(5), HC(8)), 7.11−7.03 (m, 2 H, HC(6), HC(7)), 4.74 (hept, J = 7.0 Hz, 1 H, $(H_3C)_2HC(1)$), 1.52 (d, J = 7.0 Hz, 6 H, $H_3C(10)$). ^{13}C NMR (126 MHz, $CDCl_3$) 166.6 (O=C(2)), 133.1 (N_2=CC(4)), 128.4 (N_2=C(3)), 125.2 (HC(5)), 121.6 (HC(7)), 118.5 (HC(6), 117.2 (C(9)), 110.3 (HC(8)), 44.8 ($(H_3C)_2HC(1)$), 20.2 ($H_3C(10)$); IR (ATR-FTIR) 2102 (w), 1681 (w), 1611 (w), 1467 (w), 1408 (w), 1379 (w), 1366 (w), 1345 (w), 1297 (w), 1201 (w), 1159 (w), 1129 (w), 1093 (w), 1012 (w), 818 (w), 748 (m), 698 (w), 566 (w), 566 (w), 510 (w), 499 (w); calcd for $C_{11}H_{12}N_3O$ 202.0980, found 202.0980; TLC R_f 0.51 (silica gel, 4:1 hexanes/EtOAc) [UV, I_2].



*Preparation of 3-[(3-Methylbut-2-en-1-yl)oxy]-1-isopropyl-2-oxindolone (**12c**).* To a flame-dried, 25-mL Schlenk flask fitted with a magnetic stir bar and septum were added rhodium(II) acetate dimer (8.8 mg, 0.02 mmol, 1 mol %), dichloromethane (12.7 mL), and 3-methylbut-2-en-1-ol (0.26 mL, 2.58 mmol, 1.3 equiv) under Ar to give a blue-green homogeneous solution. To a separate flame-dried, 25-mL conical flask with Ar inlet were added 1-isopropyl-3-diazoindolin-2-one (400.0 mg, 2.00 mmol, 1.0 equiv) and dichloromethane (4.0 mL) to give a deep red solution. The solution containing the diazo compound was taken up in a 5.0 mL gas-tight syringe and set up in a syringe pump for dropwise addition. The diazo compound was added over 4 h dropwise (1.0 mL/min) at rt, over which time the reaction mixture does not change color. After full addition, the reaction was stirred at rt for an additional 0.5 h, at which time complete consumption of the diazo compound was observed by TLC analysis (4:1 hexanes/EtOAc). The reaction was diluted with 1:1 hexanes/EtOAc (10 mL) and filtered through a silica plug to remove metal catalyst (4 cm × 4 cm),

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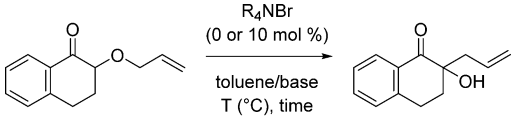
and the crude mixture was concentrated by rotary evaporation (15 mmHg) to yield the crude product as an yellow oil (850 mg). Purification by flash chromatography (SiO_2, 25 mm × 170 mm, Celite load, 10 mL fractions, hexanes/EtOAc gradient elution: 20:1 (200 mL) to 10:1 (500 mL)) yielded the desired compound as a yellow oil that eventually solidified to an orange-yellow waxy solid (467.6 mg, 91%). An analytical sample was obtained by recrystallization from boiling hexanes to yield small cubic pale yellow crystals. Data for **12c**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (d, J = 7.4 Hz, 1 H, HC(5)), 7.27 (tt, J = 7.8, 1.1 Hz, 1 H, HC(7)), 7.04 (tt, J = 7.4, 1.1 Hz, 1 H, HC(6)), 6.96 (d, J = 7.8 Hz, 1 H, HC(8)), 5.43 (dddd, J = 6.9, 5.5, 2.8, 1.3 Hz, 1 H, HC(12)), 4.83 (s, 1 H, HC(3)), 4.59 (hept, J = 7.0 Hz, 1 H, Me_2HC(1)), 4.31 (dd, J = 11.2, 6.8 Hz, 1 H, H_2C(11)), 4.25 (dd, J = 11.2, 7.4 Hz, 1 H, H_2C(11)), 1.75 (s, 3 H, H_3C(14)), 1.68 (s, 3 H, H_3C(14)), 1.46 (d, J = 7.0 Hz, 3 H, H_3C(10)), 1.46 (d, J = 7.0 Hz, 3 H, H_3C(11)); ^{13}C NMR (126 MHz, $CDCl_3$) 174.8 (O═C(2)), 143.0 (C(9)), 139.0 (C(13)), 129.6 (HC(7)), 126.1 (C(4)), 125.6 (HC(5)), 122.4 (HC(6)), 120.5 (HC(12)), 110.1 (HC(8)), 74.6 (HC(3), 65.2 (H_2C(11)), 43.8 (Me_2HC(1)), 26.0 (H_3C(14)), 19.5 (H_3C(10)), 19.4 (H_3C(10)), 18.2 (H_3C(14)); IR (ATR-FTIR) 2983 (w), 2930 (w), 2867 (w), 2849 (w), 1707 (m), 1610 (m), 1467 (m), 1355 (m), 1311 (w), 1231 (w), 1199 (w), 1128 (m), 1083 (w), 958 (w), 757 (m), 695 (w), 593 (w), 472 (w); LRMS (ES$^+$, TOF) 132.0 (18), 174.1 (89), 175.1 (18), 192.1 (95), 193.1 (13), 260.2 (100), 261.1 (17); HRMS (ESI, $[M + 1]^+$) calcd for $C_{16}H_{22}NO_2$ 260.1651, found 260.1652; TLC R_f 0.19 (silica gel, 10:1 hexanes/TBME) [UV]. Anal. Calcd for $C_{16}H_{21}NO_2$ (259.35): C, 74.10; H, 8.16; N, 5.40. Found: C, 74.34; H, 7.99; N, 5.38.

6.3. General Procedure for Phase-Transfer Catalyzed [2,3]-Rearrangement of 2-(Allyloxy)-1-tetralone.

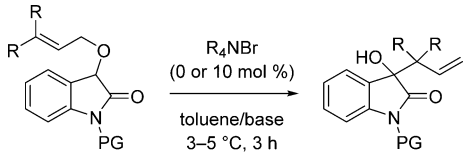


10 11

For Reactions Using Solid Base. To a 1-dram glass vial equipped with a plastic screw cap, Teflon septum, and 1.5 cm × 0.5 cm football-shaped stir bar were added quaternary ammonium bromide (10 mol %) and solid base (3.0 equiv). A stock solution of 2-(allyloxy)-1-tetralone in toluene (25 mg/0.4 mL, 0.308 M) was prepared under Ar in a separate scintillation vial. Under an inert atmosphere for argon, 2-(allyloxy)-1-tetralone was added as a stock solution (0.4 mL, 0.123 mmol, 1.0 equiv), and additional toluene was added (0.34 mL). The Ar inlet was removed, and the reaction was stirred (1600 rpm) at rt. After complete conversion of the starting material by TLC analysis (4:1 hexanes/EtOAc), the reaction was diluted by the addition of distilled water (0.2 mL) and EtOAc (0.5 mL). The organic layer was removed by syringe, and the aqueous layer was extracted with EtOAc (3 × 0.5 mL). The combined organic layer was passed through a pipet containing silica (4 cm) using EtOAc to yield a crude yellow oil. Conversion was assessed by ^{1}H NMR spectroscopic analysis by relative integration of the internal vinyl signal of starting material and product using a long delay (d1 = 15 s).

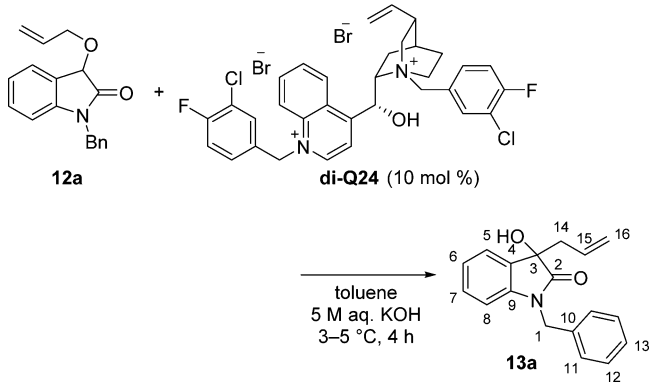
For Reactions Using Aqueous Base Solution. To a 1-dram glass vial equipped with a plastic screw cap, Teflon septum, and 1.5 cm × 0.5 cm football-shaped stir bar was added quaternary ammonium bromide (10 mol %). A stock solution of 2-(allyloxy)-1-tetralone in toluene (25 mg/0.4 mL, 0.308 M) was prepared under Ar in a separate scintillation vial. Under an inert atmosphere of argon, 2-(allyloxy)-1-tetralone was added as a stock solution (0.4 mL, 0.123 mmol, 1.0 equiv), and additional toluene was added (0.34 mL). The Ar inlet was removed, and the reaction was stirred (1500 rpm) at rt or cooled in a cold room (3−5 °C) for 25 min. After temperature equilibration, stirring was halted and aqueous base solution was added by syringe. The reaction was then stirred (1600 rpm) for the specified amount of time. The reaction was then diluted by the addition of distilled water (0.2 mL) and EtOAc (0.5 mL). The organic layer was removed by syringe, and the aqueous layer was extracted with EtOAc (3 × 0.5 mL). The combined organic layer was passed through a pipet containing silica (4 cm) using EtOAc to yield a crude yellow oil. Conversion was assessed by ^{1}H NMR spectroscopic analysis by relative integration of the internal vinyl signal of starting material and product using a long delay (d1 = 15 s). Enantiomeric ratios were determined by chiral stationary phase SFC analysis (SFC t_R 10.18 min (minor); t_R 11.19 min (major); CHIRALPAK AD, 98.5:1.5 CO_2(sc)/MeOH, 2.5 mL/min, 200 bar, 254 nm, 40 °C). The ^{1}H NMR spectroscopic data of thus obtained **11** matched that from an alternative preparation.[58] Data for **11**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.01 (dd, J = 1.6, 7.8 Hz, 1 H), 7.53 (td, J = 1.5, 7.5 Hz, 1 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.26 (d, J = 7.7 Hz, 1 H), 5.87 (dddd, J = 6.2, 8.2, 10.3, 16.7 Hz, 1 H), 5.16 (dt, J = 1.1, 10.1 Hz, 1 H), 5.08 (dd, J = 1.7, 17.1 Hz, 1 H), 3.83 (br s, 1 H), 3.10 (ddd, J = 5.1, 12.6, 17.7 Hz, 1 H), 2.98 (ddd, J = 2.4, 5.7, 17.8 Hz, 1 H), 2.44 (dd, J = 8.2, 14.1 Hz, 1 H), 2.39−2.31 (m, 2 H), 2.16 (td, J = 5.7, 13.0 Hz, 1 H); TLC R_f 0.34 (silica gel, 4:1 hexanes/EtOAc) [UV, CAM].

6.4. General Procedure for Phase-Transfer-Catalyzed [2,3]-Rearrangement of 3-(Alkenyloxy)-2-oxindolones.



12a-c 13a-c

Small-Scale Reactions for Testing Conditions and Catalysts. To a 1-dram glass vial equipped with a plastic screw cap, Teflon septum, and 1.5 cm × 0.5 cm football-shaped stir bar were added 3-(alkenyloxy)-2-oxindolone (20−25 mg, 1.0 equiv) and tetrabutylammonium bromide (10 mol %). The vial was evacuated and backfilled with Ar twice. Sparged toluene was added (0.16 M), and the reaction was stirred within a cold room for 30 min to equilibrate temperature, and then a sparged, aqueous KOH solution was added by syringe (5 or 2 M, 10.0 equiv). The reaction was stirred rapidly (1600 rpm) for 3 h at 3−5 °C. After 3 h, the reaction was quenched at 3−5 °C by the addition of 5 M aq AcOH (10 equiv). The reaction was then diluted by the addition of 0.3 mL of distilled water and 1.0 mL of EtOAc. The organic layer was removed, and the aqueous layer was extracted with EtOAc (2× 0.5 mL) and then passed through a short plug of silica and Na_2SO_4 (pipet, 6 cm) and concentrated by rotary evaporation. Conversion was determined by relative integration of starting material and product signals in the crude ^{1}H NMR ($CDCl_3$) to an internal standard (hexamethyldisilane) using an extended delay (d1 = 15 s). Enantiomeric ratios were determined by chiral stationary phase HPLC as indicated below.



12a di-Q24 (10 mol %) 13a

*Preparation of 1-Benzyl-3-(allyloxy)-2-oxindolone (**13a**).* To a 1-dram glass vial equipped with a plastic screw cap, Teflon septum, and 1.5 cm × 0.5 cm football-shaped stir bar were added 3-(allyloxy)-2-oxindolone (55.9 mg, 0.20 mmol, 1.0 equiv) and *N,N′*-(3-chloro-4-fluorobenzyl)cinchonidinium dibromide (14.8 mg, 0.02 mmol, 10 mol %). The vial was evacuated and backfilled with Ar twice. Sparged toluene was added (1.2 mL, 0.16 M), the reaction was stirred within a cold room for 30 min to equilibrate temperature, and then a sparged aqueous 5 M KOH solution was added by syringe (0.40 mL, 2.00

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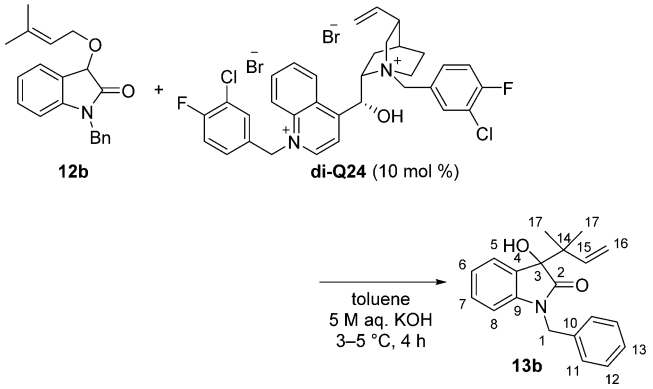
mmol, 10.0 equiv). The reaction was stirred rapidly (1600 rpm) for 3 h at 3−5 °C. After 3 h, the reaction was quenched at 3−5 °C by the addition of 5 M aq AcOH (0.40 mL, 10 equiv). The reaction was then diluted by the addition of 0.3 mL of distilled water and 1.0 mL of EtOAc. The organic layer was removed, and the aqueous layer was extracted with EtOAc (2× 1.0 mL) and then passed through a short plug of silica and Na_2SO_4 (pipet, 6 cm) and concentrated by rotary evaporation to give the crude material as a pale yellow solid (56.0 mg, quant.). Purification by column chromatography (SiO_2, 10 mm × 140 mm, 5 mL fractions, isocratic elution (4:1 hexanes/EtOAc), 40 fractions total) yielded 3-allyl-3-hydroxy-1-benzyloxindol-2-one as a white solid (50.3 mg, 90%). The enantiomeric ratio was determined after column chromatography by chiral stationary phase HPLC (67:33). An analytical sample was obtained by recrystallization. The white solid (25 mg) was taken up in a minimum of boiling hexanes (20 mL), and isopropyl alcohol was added dropwise until the turbidity diminished to give a homogeneous solution (0.1 mL). This solution was allowed to cool to rt over 3 h, at which time crystal formation was evident. The flask was then cooled to −20 °C overnight (18 h). The white crystals were collected by Büchner filtration, rinsed with an excess of cold (−20 °C) hexanes, transferred to a No-Chromix washed scintillation vial, crushed with a spatula, and dried under reduced pressure (0.1 mmHg) at rt for 24 h to yield a fine white powder (13.4 mg, 53% recovery). The enantiomeric ratio measured after recrystallization was diminished (50:50 er), and the mother liquor was enriched (97:3 er). The major enantiomer was determined to have the (*R*)-configuration by comparison to the reported elution order by HPLC under identical conditions. Krische et al. report the (*R*)-enantiomer to elute first (t_R 13.5 min) and the (*S*)-enantiomer to elute second (t_R 24.9 min) when submitted to chiral stationary phase HPLC (CHIRALCEL OJ-H, 90:10 hexane/isopropyl alcohol, 0.8 mL/min, 245 nm, 23 °C) and confirm this absolute configuration by X-ray crystallography. When identical HPLC conditions were used in this experiment, the major enantiomer eluted first (t_R 15.6 min). See the Supporting Information for the HPLC chromatogram.[60] Data for **13a**: mp 151−152 °C (from hexanes/*i*-PrOH); ^{1}H NMR (500 MHz, $CDCl_3$) 7.40 (d, *J* = 7.3 Hz, 1 H, HC(5)), 7.33−7.23 (m, 5 H, HC(11,12,13)), 7.20 (td, *J* = 1.3, 7.8 Hz, 1 H, HC(7)), 7.06 (t, *J* = 7.6 Hz, 1 H, HC(6)), 6.70 (d, *J* = 7.8 Hz, 1 H, HC(8)), 5.66 (ddddd, *J* = 2.1, 6.2, 8.4, 10.5, 16.8 Hz, 1 H, HC(15)), 5.15 (dt, *J* = 1.5, 17.1 Hz, 1 H, H_2C(16)), 5.10 (dd, *J* = 2.1, 10.2 Hz, 1 H, H_2C(16)), 5.02 (dd, *J* = 2.3, 15.8 Hz, 1 H, H_2C(1)), 4.73 (d, *J* = 15.8 Hz, 1 H, H_2C(1)), 3.28 and 3.20 (br s, 1 H OH), 2.82 (dd, *J* = 6.3, 13.3 Hz, 1 H, H_2C(14)), 2.70 (dd, *J* = 8.5, 13.3 Hz, 1 H, H_2C(14)); ^{13}C NMR (126 MHz, $CDCl_3$) 178.0 (O═C(2)), 142.6 (C(9)), 135.5 (C(10)), 130.6 (HC(15)), 129.7 (HC(7)), 129.7 (C(4)), 128.9 (HC(11,12)), 127.8 (HC(13)), 127.4 (HC(11,12)), 124.3 (HC(5)), 123.2 (HC(6)), 120.7 (H_2C(16)), 109.6 (HC(8)), 76.1 (C(3)), 44.0 (H_2C(1)), 43.2 (H_2C(14)); IR (ATR-FTIR) 3283 (w), 3078 (w), 3033 (w), 2981 (w), 2906 (w), 1693 (m), 1641 (w), 1615 (w), 1495 (w), 1470 (m), 1389 (w), 1375 (w), 1358 (m), 1289 (w), 1228 (w), 1180 (m), 1137 (w), 1113 (w), 1079 (m), 1029 (w), 989 (m), 918 (m), 779 (w), 649 (m); LRMS (ES$^+$, TOF) 262.1 (100), 263.1 (20), 280.1 (52), 281.1 (10); HRMS (ESI, $[M + 1]^+$) calcd for $C_{18}H_{18}NO_2$ 280.1338, found 280.1341; TLC R_f 0.03 (silica gel, 10:1 hexanes/TBME) [UV, I_2]; HPLC (*R*)-**13a**, t_R 15.6 min (67%); (*R*)-**13a** t_R 20.8 min (33%) (CHIRALCEL OJ-H, 90:10 hexane/isopropyl alcohol, 0.8 mL/min, 245 nm, 23 °C). Anal. Calcd for $C_{18}H_{17}NO_2$ (279.34): C, 77.40; H, 6.13; N, 5.01. Found: C, 77.20; H, 6.21; N, 4.91.



*Preparation of 1-Benzyl-3-[(2-methylbut-3-en-2-yl)oxy]-2-oxindolone (**13b**).* To a 1-dram glass vial equipped with a plastic screw cap, Teflon septum, and 1.5 cm × 0.5 cm football-shaped stir bar was added *N*,*N*′-(3-chloro-4-fluorobenzyl)cinchonidinium dibromide (14.8 mg, 0.02 mmol, 10 mol %). The vial was evacuated and backfilled with Ar twice. To a separate 1-dram glass vial equipped with a plastic screw cap and Teflon septum was added 1-benzyl-3-((3-methylbut-2-en-1-yl)oxy)indolin-2-one (61.5 mg, 0.2 mmol, 1.0 equiv). The vial was evacuated and backfilled with Ar twice, and then the starting material was taken up in sparged toluene (0.5 mL). This stock solution was transferred to the vial containing catalyst by syringe, and then the vial previously containing the starting material was rinsed with the remaining toluene (0.7 mL). The reaction vial was stirred within a cold room for 30 min to equilibrate temperature, and then a sparged aqueous 5 M KOH solution was added by syringe (0.40 mL, 2.00 mmol, 10.0 equiv). The reaction was stirred rapidly (1600 rpm) for 3 h at 3−5 °C. After 3 h, the reaction was quenched at 3−5 °C by the addition of 5 M aq AcOH (0.40 mL, 10 equiv). The reaction was then diluted by the addition of 0.3 mL of distilled water and 1.0 mL of EtOAc. The organic layer was removed, and the aqueous layer was extracted with EtOAc (2 × 1.0 mL) and then was passed through a short plug of silica and Na_2SO_4 (pipet, 6 cm) and concentrated by rotary evaporation to give the crude material as a red-brown oil. Purification by column chromatography (SiO_2, 10 mm × 180 mm, 5 mL fractions, gradient elution (hexanes/EtOAc: 10:1 (250 mL) to 4:1 (100 mL) to 3:1 (100 mL)), 50 fractions total) yielded 3-allyl-3-hydroxy-1-benzyloxindol-2-one as a pale yellow solid (50.3 mg, 90%). The enantiomeric ratio was determined after column chromatography by chiral stationary phase HPLC. An analytical sample was obtained by recrystallization. The pale yellow solid (35 mg) was taken up in a minimum of boiling hexanes (20 mL). This solution was allowed to cool to rt over 3 h, at which time crystal formation was evident. The flask was then cooled to −20 °C overnight (18 h). The white crystals were collected by Büchner filtration, rinsed with an excess of cold (−20 °C) hexanes, transferred to a No-Chromix washed scintillation vial, crushed with a spatula, and dried under reduced pressure (0.1 mmHg) at rt for 24 h to yield a fine white needles (18.1 mg, 51% recovery). The enantiomeric ratio measured after recrystallization was slightly enriched (70:30 er) and the mother liquor was diminished (55:45 er). Data for **13b**: mp 92−94 °C (from hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 7.41 (dd, *J* = 1.4, 7.5 Hz, 1 H, HC(5)), 7.34−7.24 (m, 5 H, HC(11,12,13)), 7.22−7.14 (m, 2 H, HC(6), HC(11,12,13)), 7.02 (td, *J* = 1.0, 7.6 Hz, 1 H, HC(7)), 6.70 (dd, *J* = 0.7, 7.9 Hz, 1 H, HC(8)), 6.18 (dd, *J* = 10.8, 17.5 Hz, 1 H, HC(15)), 5.22 (dd, *J* = 1.4, 10.8 Hz, 1 H, H_2C(16)), 5.15 (dd, *J* = 15.6 Hz, 1 H, H_2C(16)), 5.06 (d, *J* = 15.6 Hz, 1 H, H_2C(1)), 4.65 (d, *J* = 15.6 Hz, 1 H, H_2C(1)), 2.82 (br s, 1 H, OH), 1.21 (s, 3 H, H_3C(17)), 1.13 (S, 3 H, H_3C(17)); ^{13}C NMR (126 MHz, $CDCl_3$) 178.1 ((O═C(2)), 143.7 (C(4)), 142.1 (HC(15)), 135.8 (C(9)), 129.6 (HC(6)), 128.9 (HC(11,12)), 127.8 (HC(13)), 127.5 (HC(11,12)), 126.1 (HC(5)), 122.4 (HC(7)), 115.8 (H_2C(16)), 109.2 (HC(8)), 80.1 (C(3)), 44.1 (H_2C(1)), 43.9 (C(14)), 22.4 (H_3C(17)), 20.2 (H_3C(17)); IR (ATR-FTIR) 3394 (w), 3072 (2), 3059 (w), 3028 (w), 2969 (w), 1692 (m), 1605 (w), 1467 (w), 1368 (w), 1340 (w), 1186 (w), 1119 (w), 1003 (w), 909 (w), 740 (m), 695 (m); LRMS (ES$^+$, TOF) 248.1 (18), 266.1 (40),

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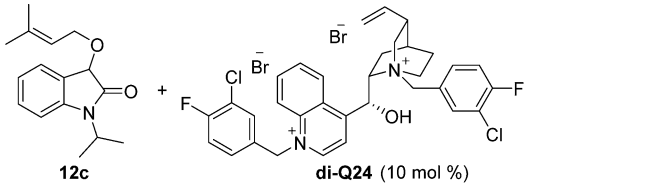
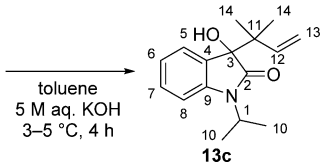
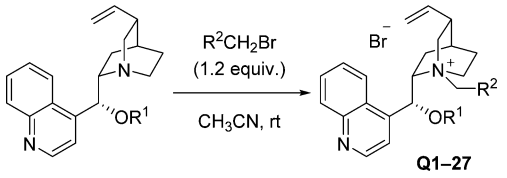
290.2 (55), 291.2 (13), 308.2 (100), 309.2 (18); HRMS (ESI, [M + 1]$^+$) calcd for $C_{20}H_{22}NO_2$ 308.1651, found 308.1653; TLC R_f 0.04 (silica gel, 10:1 hexanes/TBME) [UV, I_2]. HPLC t_R 13.9 min (64%); t_R 17.2 min (36%) (CHIRALPAK AD-H, 82:18 hexane/isopropyl alcohol, 0.5 mL/min, 220 nm, 15 °C). Anal. Calcd for $C_{20}H_{21}NO_2$ (307.39): C, 78.15; H, 6.89; N, 4.56. Found: C, 77.87; H, 6.99; N, 4.50.



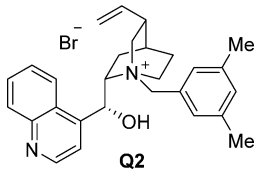


*Preparation of 1-Isopropyl-3-(2-methylbut-3-en-2-yl)oxy-2-oxindolone (**13c**).* To a 1-dram glass vial equipped with a plastic screw cap, Teflon septum, and 1.5 cm × 0.5 cm football-shaped stir bar was added *N*,*N*′-(3-chloro-4-fluorobenzyl)cinchonidinium dibromide (14.8 mg, 0.02 mmol, 10 mol %). The vial was evacuated and backfilled with Ar twice. To a separate 1-dram glass vial equipped with a plastic screw cap and Teflon septum was added 1-isopropyl-3-((3-methylbut-2-en-1-yl)oxy)indolin-2-one (61.5 mg, 0.2 mmol, 1.0 equiv). The vial was evacuated and backfilled with Ar twice, and then the starting material was taken up in sparged toluene (0.5 mL). This stock solution was transferred to the vial containing catalyst by syringe, and then the vial containing the starting material was rinsed with the remaining toluene (0.7 mL). The reaction vial was stirred within a cold room for 30 min to equilibrate temperature, and then a sparged aqueous 5 M KOH solution was added by syringe (0.40 mL, 2.00 mmol, 10.0 equiv). The reaction was stirred rapidly (1600 rpm) for 3 h at 3−5 °C. After 3 h, the reaction was quenched at 3−5 °C by the addition of 5 M aq AcOH (0.40 mL, 10 equiv). The reaction was then diluted by the addition of 0.3 mL of distilled water and 1.0 mL of EtOAc. The organic layer was removed,and the aqueous layer was extracted with EtOAc (2× 1.0 mL), passed through a short plug of silica and Na_2SO_4 (pipet, 6 cm), and concentrated by rotary evaporation to give the crude material as a red-brown oil. Purification by column chromatography (SiO_2, 10 mm × 180 mm, 5 mL fractions, gradient elution (hexanes/EtOAc: 10:1 (250 mL) to 4:1 (100 mL) to 3:1 (100 mL)), 50 fractions total) yielded 3-allyl-3-hydroxy-1-isopropyloxindol-2-one as a very thick yellow oil (52.0 mg, quant.). An analytical sample was obtained by distillation (air bath = 140 °C, 3.2 × 10^{-5} mm Hg). Data for **13c**: bp 140 °C (air, 3.2 × 10^{-5} mm Hg); ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (br d, *J* = 7.4 Hz, 1 H, HC(5)), 7.26 (td, *J* = 1.2, 7.8 Hz, 1 H, HC(7)), 7.00 (td, *J* = 1.0, 7.6 Hz, 1 H, HC(6)), 6.93 (d, *J* = 7.9 Hz, 1 H, HC(8)), 6.11 (dd, *J* = 10.8, 17.5 Hz, 1 H, HC(12)), 5.17 (dd, *J* = 1.4, 10.8 Hz, 1 H, H_2C(13)), 5.09 (dd, *J* = 1.4, 17.5 Hz, 1 H, H_2C(13)), 4.51 (hept, *J* = 7.0 Hz, 1 H, HC(1)), 2.84 (br s, 1 H, OH), 1.45 (t, *J* = 6.6 Hz, 6 H, H_3C(10), 1.14 (s, 3 H, H_3C(14)), 1.07 (s, 3 H, H_3C(14)); ^{13}C NMR (126 MHz, $CDCl_3$) 177.6 (O═C(2)), 143.0 (C(4)), 142.1 (HC(12)), 129.3 (HC(6)), 128.9 (C(9)), 126.2 (HC(5)), 121.7 (HC(7)), 115.4 (H_2C(13)), 109.5 (HC(8)), 79.6 (C(3)), 44.0 (HC(1)), 43.9 (C(11), 22.2 (H_3C(14)), 20.0 (H_3C-(14)), 19.5 (H_3C(10)), 19.2 (H_3C(10)); IR (ATR-FTIR) 3435 (w), 3086 (w), 3055 (w), 2979 (w), 2939 (w), 2876 (w), 1699 (s), 1610 (m), 1467 (m), 1359 (w), 1320 9w), 1195 (w), 1106 (w), 1003 (w), 914 (w), 757 (m), 744 (m); LRMS (ES$^+$, TOF) 200.1 (60), 201.1 (12), 242.2 (47), 243.2 (7), 260.2 (100), 261.2 (15), 282.1 (42), 283.2 (6); HRMS (ESI, [M + 1]$^+$) calcd for $C_{16}H_{22}NO_2$ 260.1651, found 260.1654; TLC R_f 0.12 (silica gel, 10:1 hexanes/TBME) [UV, I_2]; HPLC t_R 10.1 min (65%), t_R 12.0 min (35%) (CHIRALPAK AD-H, 82:18 hexane/isopropyl alcohol, 0.5 mL/min, 220 nm, 15 °C).

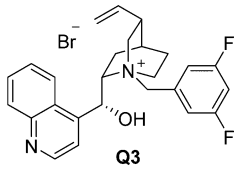
6.5. General Procedure for the Preparation of Monoquaternized Phase-Transfer Catalysts.



In a 25 mL, two-necked, round-bottomed flask containing a magnetic stir bar and argon inlet were combined *O*-alkylated cinchonidine (1.0 equiv) and acetonitrile (0.10 M). To the reaction mixture was added α-bromoarylmethane (1.2 equiv) and the mixture stirred under argon for 24−72 h at room temperature. After complete consumption of *O*-alkylated cinchonidine as determined by TLC (9:1 EtOAc/triethylamine and 10:1 CH_2Cl_2/MeOH), the reaction mixture was diluted with 4 mL of dichloromethane, Celite was added, and the material was concentrated to dryness. The crude material was then purified directly by silica gel chromatography (dry loaded in pure CH_2Cl_2, 30 mm × 210 mm, CH_2Cl_2/MeOH, 20:1 (200 mL) →10:1 (600 mL). The purified fractions were concentrated and then were triturated successively with hexanes and TBME to obtain a free-flowing powder, which was dried at rt under reduced pressure (0.1 mmHg) and used without further purification. The ^{1}H NMR spectroscopic data of thus obtained catalysts matched that for previously reported preparation of **Q1**,[61] **Q5**,[62] **Q6**,[63] **Q7**,[61] **Q8**,[61] and **Q10**−**Q13**.[61] Quaternary ammonium salts **Q14** and **Q15** were prepared as previously reported by these laboratories.[64] Salt **Q16** was purchased from Sigma-Aldrich and used as received.



*Data for **Q2**:*[65] ^{1}H NMR (500 MHz, DMSO-d_6) 8.97 (d, *J* = 4.5 Hz, 1 H), 8.25 (d, *J* = 8.9 Hz, 1 H), 8.10 (dd, *J* = 1.4, 8.4 Hz, 1 H), 7.84 (ddd, *J* = 1.3, 6.8, 8.4 Hz, 1 H), 7.78 (d, *J* = 4.5 Hz, 1 H), 7.74 (ddd, *J* = 1.4, 6.8, 8.4 Hz, 1 H), 7.28 (br s, 2 H), 7.18 (br s, 1 H), 6.70 (d, *J* = 4.3 Hz, 1 H), 6.51 (br d, *J* = 4.4 Hz, 1 H), 5.66 (ddd, *J* = 6.5, 10.5, 17.2 Hz, 1 H), 5.14 (dt, *J* = 1.3, 17.3 Hz, 1 H), 4.98 (d, *J* = 12.8 Hz, 1 H), 4.95 (d, *J* = 11.1 Hz, 1 H), 4.87 (d, *J* = 12.2 Hz, 1 H), 4.26−4.14 (m, 1 H), 3.86 (t, *J* = 8.8 Hz, 1 H), 3.65 (dt, *J* = 3.5 Hz, 12.2 Hz, 1 H), 3.30−3.21 (m, 2 H), 2.72−2.63 (m, 1 H), 2.14−2.00 (m, 2 H), 1.99−1.94 (m, 1 H), 1.86−1.74 (m, 1 H), 1.27 (t, *J* = 11.4 Hz, 1 H).



*Data for **Q3**:*[66] ^{1}H NMR (500 MHz, DMSO-d_6) 8.97 (d, *J* = 4.4 Hz, 1 H), 8.27 (d, *J* = 8.7 Hz, 1 H), 8.10 (dd, *J* = 1.5, 8.4 Hz, 1 H), 7.84 (ddd, *J* = 1.3, 6.9, 8.5 Hz, 1 H), 7.79 (d, *J* = 4.5 Hz, 1 H), 7.74 (ddd, *J* = 1.3, 6.8, 8.4 Hz, 1 H), 7.57 (dd, *J* = 2.4, 8.1 Hz, 2 H), 7.53 (ddt, *J* = 2.6, 9.3, 11.6 Hz, 1 H), 6.70 (d, *J* = 4.3 Hz, 1 H), 6.49 (br s, 1 H), 5.66 (ddd, *J* = 6.3, 10.6, 17.2 Hz, 1 H), 5.16 (d, *J* = 16.7 Hz, 1 H), 5.13 (d, *J* = 12.0 Hz, 1 H), 5.03 (d, *J* = 12.4 Hz, 1 H), 4.94 (d, *J* = 10.6 Hz, 1 H), 4.33−4.23 (m, 1 H), 3.86 (t, *J* = 8.8 Hz, 1 H), 3.74 (dt, *J* = 3.8, 12.5 Hz, 1 H), 3.40−3.25 (m, 2 H), 2.69−2.61 (m, 1 H), 2.14−2.01 (m, 2 H), 1.99 (q, *J* = 3.7 Hz, 1 H), 1.84−1.75 (m, 1 H), 1.27 (ddd, *J* = 3.0, 7.9, 11.8 Hz, 1 H).

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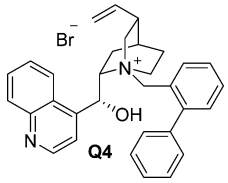
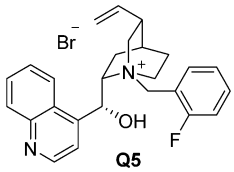


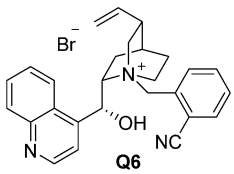
Q4

Data for **Q4**: ^{1}H NMR (500 MHz, $CDCl_3$) 8.86 (d, *J* = 4.5 Hz, 1 H), 8.28 (d, *J* = 7.6 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.83−7.77 (m, 2 H), 7.64 (t, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.3 Hz, 4 H), 7.60−7.48 (m, 4 H), 7.37 (d, *J* = 7.5 Hz, 1 H), 6.75 (br d, *J* = 6.8 Hz, 1 H), 6.43−6.32 (m, 2 H), 5.35−5.23 (m, 1 H), 5.14 (d, *J* = 12.2 Hz), 4.85 (d, *J* = 10.6 Hz, 1 H), 4.75 (br s, 1 H), 4.68 (d, *J* = 17.2 Hz, 1 H), 3.26 (br t, *J* = 9.1 Hz, 1 H), 3.12 (td, *J* = 5.9, 11.6 Hz, 1 H), 2.98 (t, *J* = 11.4 Hz, 1 H), 2.46−2.28 (m, 2 H), 2.24−2.12 (m, 1 H), 2.08−1.99 (m, 1 H), 1.91−1.86 (m, 1 H), 1.66 (br t, *J* = 14.2 Hz, 1 H), 1.07 (t, *J* = 11.9 Hz, 1 H).



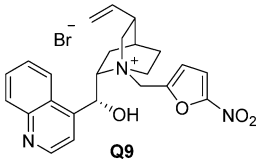
Q5

Data for **Q5**:[62] ^{1}H NMR (500 MHz, MeOH-d_4) 8.96 (d, *J* = 4.6 Hz, 1 H), 8.31 (d, *J* = 8.5 Hz, 1 H), 8.13 (dd, *J* = 8.4, 1.3 Hz, 1 H), 7.97 (dd, *J* = 4.6, 0.9 Hz, 1 H), 7.90−7.79 (m, 3 H), 7.67 (tdd, *J* = 7.4, 5.3, 1.8 Hz, 1 H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.38 (ddd, *J* = 9.7, 8.4, 1.1 Hz, 1 H), 6.67 (br d, *J* = 2.4 Hz, 1 H), 5.70 (ddd, *J* = 15.7, 10.5, 6.9 Hz, 1 H), 5.35 (d, *J* = 12.7 Hz, 1 H), 5.16 (d, *J* = 17.2 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1 H), 4.99 (d, *J* = 12.4 Hz, 1 H), 4.51 (ddt, *J* = 11.7, 8.0 4.3 Hz, 1 H), 4.06 (t, *J* = 9.2 Hz, 1 H), 3.70 (dt, *J* = 12.5, 4.0 Hz, 1 H), 3.57 (dd, *J* = 12.7, 10.5 Hz, 1 H), 3.36−3.27 (m, 1 H), 2.79−2.70 (m, 1 H), 2.33−2.20 (m, 2 H), 2.08 (br q, *J* = 3.3 Hz, 1 H), 1.95−1.84 (m, 1 H), 1.42 (ddt, *J* = 13.6, 10.1, 3.3 Hz, 1 H); ^{13}C NMR 126 MHz, MeOH-d_4) 163.7 (d, J_{C-F} = 249.5 Hz), 151.0, 148.7, 147.5, 138.7, 136.9 (d, J_{C-F} = 2.0 Hz), 134.7 (d, J_{C-F} = 9.0 Hz), 131.2, 130.2, 129.2, 126.4 (d, J_{C-F} = 3.5 Hz), 126.1, 124.1, 121.3, 117.6 (d, J_{C-F} = 22.4 Hz), 117.5, 116.2 (d, J_{C-F} = 13.6 Hz), 69.7, 66.4, 62.1, 58.5, 52.9, 39.2, 27.8, 26.0, 22.6; ^{19}F NMR (470 MHz, MeOH-d_4) −113.5 (q, *J* = 9.4 Hz); LRMS (ES^+) 111.3 (17), 202.4 (2), 212.9 (2), 327.1 (2), 403.4 (100), 404.4 (30), 405.3 (12), 406.4 (2); HRMS (ESI, $[M]^+$) calcd for $C_{26}H_{28}N_2OF^+$ 403.2186, found 403.2188.



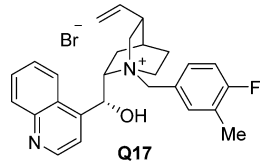
Q6

Data for **Q6**:[63] ^{1}H NMR (500 MHz, DMSO-d_6) 8.98 (d, *J* = 4.5 Hz, 1 H), 8.34 (d, *J* = 8.4 Hz, 1 H), 8.13−8.08 (m, 3 H), 7.95 (td, *J* = 1.5, 7.7 Hz, 1 H), 7.87−7.77 (m, 3 H), 7.74 (ddd, *J* = 1.4, 6.8, 8.3 Hz, 1 H), 6.87 (d, *J* = 2.7 Hz, 1 H), 6.56 (br s, 1 H), 5.67 (ddd, *J* = 6.4, 10.6, 17.2 Hz, 1 H), 5.33 (d, *J* = 13.2 Hz, 1 H), 5.24 (d, *J* = 12.9 Hz, 1 H), 5.18 (dt, *J* = 1.4, 17.3 Hz, 1 H), 4.95 (dd, *J* = 1.4, 10.6 Hz, 1 H), 4.50−4.39 (m, 1 H), 4.03 (t, *J* = 9.3 Hz, 1 H), 3.89 (dt, *J* = 4.0, 12.6 Hz, 1 H), 3.42 (t, *J* = 11.4 Hz, 1 H), 3.26 (dd, *J* = 3.4, 10.7 Hz, 1 H), 2.69−2.60 (m, 1 H), 2.16−2.03 (m, 2 H), 2.01−1.97 (m, 1 H), 1.84−1.73 (m, 1 H), 1.22 (t, *J* = 11.0 Hz, 1 H).



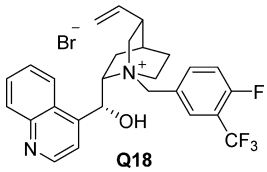
Q9

Data for **Q9**: ^{1}H NMR (500 MHz, DMSO-d_6) 8.97 (d, *J* = 4.4 Hz, 1 H), 8.26 (d, *J* = 8.2 Hz, 1 H), 8.09 (dd, *J* = 1.4, 8.5 Hz, 1 H), 7.85 (d, *J* = 3.8 Hz, 1 H), 7.84−7.80 (m, 1 H), 7.76 (d, *J* = 4.8 Hz, 1 H), 7.71 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1 H), 7.35 (d, *J* = 3.8 Hz, 1 H), 6.73 (d, *J* = 4.0 Hz, 1 H), 6.40 (br s, 1 H), 5.68 (ddd, *J* = 6.4, 10.3, 17.1 Hz, 1 H), 5.29 (d, *J* = 13.8 Hz, 1 H), 5.19 (d, *J* = 14.7 Hz, 1 H), 5.15 (d, *J* = 17.1 Hz, 1 H), 4.97 (dd, *J* = 1.3, 10.6 Hz, 1 H), 4.31−4.20 (m, 1 H), 3.94 (t, *J* = 9.2 Hz, 1 H), 3.75−3.68 (m, 1 H), 3.62 (dd, *J* = 10.2, 12.8 Hz, 1 H), 3.52−3.41 (m, 1 H), 2.73−2.62 (m, 1 H), 2.55−2.50 (m, 1 H), 2.16−2.05 (m, 2 H), 2.04−1.98 (m, 1 H), 1.88−1.76 (m, 1 H), 1.33−1.20 (m, 1 H).



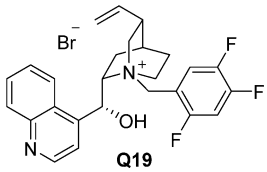
Q17

Data for **Q17**: ^{1}H NMR (500 MHz, MeOH-d_4) 8.93 (d, *J* = 4.6 Hz, 1 H), 8.32 (d, *J* = 8.3 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 1 H), 7.95 (d, *J* = 4.7 Hz, 1 H), 7.84−7.75 (m, 2 H), 7.68 (dd, *J* = 7.0, 2.6 Hz, 1 H), 7.62 (dt, *J* = 7.8, 2.7 Hz, 1 H), 7.20 (t, *J* = 8.9 Hz, 1 H), 6.64 (br s, 1 H), 5.67 (ddd, *J* = 17.2, 10.6, 6.7 Hz, 1 H), 5.22−5.14 (m, 2 H), 5.09 (d, *J* = 12.4 Hz, 1 H), 4.97 (d, *J* = 10.5 Hz, 1 H), 4.44 (ddt, *J* = 11.3, 8.3, 4.3 Hz, 1 H), 4.03 (t, *J* = 8.9 Hz), 3.77−3.70 (m, 1 H), 3.46 (t, *J* = 11.2 Hz, 1 H), 3.39 (td, *J* = 12.0, 4.8 Hz, 1 H), 2.78−2.67 (m, 1 H), 2.34 (s, 3 H), 2.28−2.19 (m, 2 H), 2.08−2.02 (m, 1 H), 1.95−1.79 (m, 1 H), 1.43−1.35 (m, 1 H). ^{13}C NMR (126 MHz, MeOH-d_4) 164.0 (d, J_{C-F} = 248.0 Hz), 151.0, 148.7, 147.5, 138.7, 138.3 (d, J_{C-F} = 5.8), 134.4 (d, J_{C-F} = 5.8 Hz), 131.2, 130.4, 129.2, 127.3 (d, J_{C-F} = 17.9 Hz), 126.1, 124.5 (d, J_{C-F} = 3.8 Hz), 124.1, 121.3, 117.5, 116.8 (d, J_{C-F} = 23f0 Hz), 69.6, 66.3, 64.4, 61.9, 52.6, 39.1, 28.0, 25.9, 22.5, 14.5; ^{19}F NMR (470 MHz, MeOH-d_4) −116.9 (br s); LRMS (ES^+) 111.3 (2), 209.3 (2), 417.4 (100), 418.4 (45), 419.4 (25), 420.4 (2); HRMS (ESI, $[M]^+$) calcd for $C_{27}H_{30}N_2OF^+$ 417.2342, found 417.2340.



Q18

Data for **Q18**: ^{1}H NMR (500 MHz, MeOH-d_4) 8.95 (d, *J* = 4.5 Hz, 1 H), 8.33 (d, *J* = 8.5 Hz, 1 H), 8.17 (dd, *J* = 6.6, 2.3 Hz, 1 H), 8.14−8.10 (m, 2 H), 7.96 (dd, *J* = 4.6, 0.9 Hz, 1 H), 7.85 (ddd, *J* = 8.4, 6.9, 1.5 Hz), 7.81 (ddd, *J* = 8.3, 6.9, 1.5 Hz, 1 H), 7.57 (dd, *J* = 10.3, 8.5 Hz, 1 H), 6.64 (br s, 1 H), 5.68 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1 H), 5.29 (d, *J* = 12.6 Hz, 1 H), 5.18 (d, *J* = 12.6 Hz, 1 H), 5.17 (d, *J* = 17.2 Hz, 1 H), 5.00 (dt, *J* = 10.5, 1.2 Hz, 1 H), 4.50 (ddp, *J* = 10.8, 8.4, 2.9 Hz, 1 H), 4.03 (ddt, *J* = 10.5, 8.4, 2.1 Hz, 1 H), 3.73 (ddd, *J* = 12.6, 4.9, 3.1 Hz, 1 H), 3.47 (dd, *J* = 12.6, 10.6 Hz, 1 H), 3.38 (tdd, *J* = 11.4, 5.0, 1.8 Hz, 1 H), 2.77−2.69 (m, 1 H), 2.33−2.19 (m, 2 H), 2.08 (q, *J* = 3.1 Hz, 1 H), 1.90 (dddd, *J* = 16.2, 11.0, 5.3, 2.7 Hz, 1 H), 1.42 (tdd, *J* = 13.5, 6.5, 3.6 Hz, 1 H); ^{13}C NMR (126 MHz, MeOH-d_4) 162.3 (d, J_{C-F} = 259.4 Hz), 151.0, 148.7, 147.4, 141.6 (d, J_{C-F} = 9.4 Hz), 138.6, 133.9 (d, J_{C-F} = 2.9 Hz), 131.2, 130.3, 129.2, 125.9, 125.8 (d, J_{C-F} = 4.0 Hz), 124.2, 123.8 (q, J_{C-F} = 272.0 Hz), 121.3, 120.0 (dd, J_{C-F} = 32.9, 13.5 Hz), 119.2 (d, J_{C-F} = 21.3 Hz), 117.6, 69.9, 66.3, 63.4, 61.8, 52.7, 39.1, 28.0, 25.9, 22.5; ^{19}F NMR (470 MHz, MeOH-d_4) −63.3 (d, *J* = 12.5 Hz, CF_3), −114.2 (dtq, *J* = 5.7, 12.5, 18.3 Hz, Ar-F); LRMS (ES^+) 111.3 (2), 236.3 (2), 471.4 (100), 472.4 (40), 473.4 (15), 747.5 (2); HRMS (ESI, $[M]^+$) calcd for $C_{27}H_{27}N_2OF_4^+$ 471.2060, found 471.2057.



Q19

Data for **Q19**: ^{1}H NMR (500 MHz, MeOH-d_4) 8.96 (d, *J* = 4.5 Hz, 1 H), 8.31 (dd, *J* = 8.4, 1.4 Hz, 1 H), 8.13 (dd, *J* = 8.6, 1.3 Hz, 1 H), 7.96 (d, *J* = 4.7 Hz, 1 H), 7.94−7.89 (m, 1 H), 7.85 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1 H), 7.81 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1 H), 6.63 (br s, 1 H),

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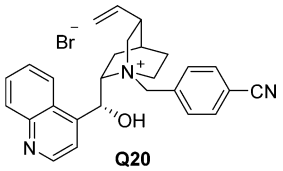
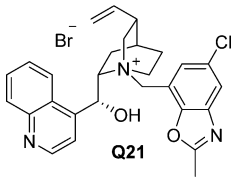
5.70 (ddd, J = 17.2, 10.5, 6.7 Hz, 1 H), 5.30 (d, J = 12.9 Hz, 1 H), 5.18 (d, J = 17.2 Hz, 1 H), 5.02−4.97 (m, 2 H), 4.49 (dddd, J = 14.7, 11.6, 7.0, 3.8 Hz, 1 H), 4.05 (br t, J = 9.2 Hz, 1 H), 3.71 (ddd, J = 12.6, 4.8, 3.0 Hz, 1 H), 3.61 (dd, J = 12.5, 10.5 Hz, 1 H), 3.37−3.30 (m, 2 H), 2.81−2.73 (m, 1 H), 2.31−2.21 (m, 2 H), 2.12−2.07 (m, 1 H), 1.91 (tdd, J = 12.7, 7.0, 4.2 Hz, 1 H), 1.44−1.36 (m, 1 H); ^{13}C NMR (126 MHz, MeOH-d_4) 159.4 (dd, J_{C-F} = 248.8, 10.1, 26 Hz), 153.5 (dt, J_{C-F} = 255.5, 14.1), 151.0, 148.7, 148.7, 148.5 (dd, J_{C-F} = 239.4, 12.2, 2.9), 147.4, 138.6, 131.2, 130.4, 129.2, 126.1, 124.4 (d, J_{C-F} = 18.0 Hz), 124.1, 121.3, 117.6, 113.0 (dt, J_{C-F} = 16.0, 4.4 Hz), 107.9 (dd, J_{C-F} = 29.3, 21.5); LRMS (ES$^+$) 111.3 (3), 439.4 (100), 440.4 (30), 441.4 (12), 442.4 (2); HRMS (ESI, [M]$^+$) calcd for $C_{26}H_{26}N_2OF_3^+$ 439.1997, found 439.1998.



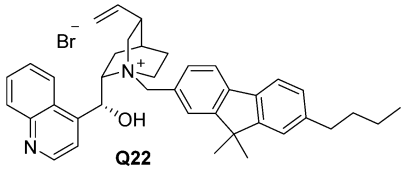
Q20

Data for ***Q20****:* ^{1}H NMR (500 MHz, DMSO-d_6) 8.97 (d, J = 4.4 Hz, 1 H), 8.31 (d, J = 8.4 Hz, 1 H), 8.09 (d, J = 8.4 Hz, 1 H), 8.06 (d, J = 8.1 Hz, 2 H), 7.98 (d, J = 8.1 Hz, 2 H), 7.83 (t, J = 7.6 Hz, 1 H), 7.80 (d, J = 4.5 Hz, 1 H), 7.74 (ddd, J = 8.4, 6.9, 1.4 Hz, 1 H), 6.75 (d, J = 4.5 Hz, 1 H), 6.53 (br s, 1 H), 5.66 (ddd, J = 17.2, 10.6, 6.4 Hz, 1 H), 5.28 (d, J = 12.2 Hz, 1 H), 5.16 (d, J = 16.9 Hz, 1 H), 5.16 (d, J = 12.6 Hz, 1 H), 4.94 (d, J = 10.3 Hz, 1 H), 4.36−4.25 (m, 1 H), 3.93 (br t, J = 8.6 Hz, 1 H), 3.82 (br d, J = 12.3 Hz, 1 H), 3.30 (dd, J = 12.2, 10.6 Hz, 1 H), 3.21 (td, J = 11.6, 5.1 Hz, 1 H), 2.68−2.60 (m, 1 H), 2.15−2.01 (m, 2 H), 2.01−1.95 (m, 1 H), 1.78 (td, J = 12.8, 12.1, 6.3 Hz, 1 H), 1.31−1.23 (m, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 150.2, 147.6, 145.1, 138.0, 134.8, 133.4, 132.7, 129.9, 129.4, 127.3, 124.3, 123.7, 120.1, 118.4, 116.4, 67.9, 64.0, 61.8, 59.3, 50.8, 36.9, 25.9, 24.2, 21.0; LRMS (ES$^+$) 111.3 (4), 295.3 (2), 410.4 (100), 411.4 (30), 412.4 (10), 413.3 (5); HRMS (ESI, [M]$^+$) calcd for $C_{27}H_{28}N_3O^+$ 410.2232, found 410.2227.



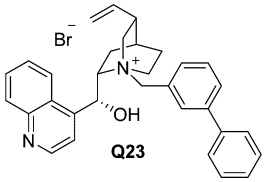
Q21

Data for ***Q21****:* ^{1}H NMR (500 MHz, MeOH-d_4) 8.96 (d, J = 4.6 Hz, 1 H), 8.33 (d, J = 8.6, 1.4 Hz, 1 H), 8.14 (dd, J = 8.4, 1.3 Hz, 1 H), 7.96 (dd, J = 4.5, 0.9 Hz, 1 H), 7.91−7.85 (m, 2 H), 7.85−7.79 (m, 2 H), 6.69 (br s, 1 H), 5.72 (ddd, J = 17.2, 10.5, 6.7 Hz, 1 H), 5.47 (d, J = 13.0 Hz, 1 H), 5.20 (d, J = 13.0 Hz, 1 H), 5.16 (d, J = 17.2 Hz, 1 H), 5.03 (d, J = 10.5 Hz, 1 H), 4.60 (dddd, J = 14.0, 11.3, 6.9, 3.9 Hz, 1 H), 4.09 (ddd, J = 10.3, 8.1, 2.3 Hz, 1 H), 3.74 (ddd, J = 12.6, 5.1, 3.0 Hz, 1 H), 3.63 (dd, J = 12.6, 10.5 Hz, 1 H), 3.43−3.34 (m, 1 H), 2.74 (ddd, J = 10.0, 4.5, 2.2 Hz, 1 H), 2.68 (s, 3 H), 2.36−2.21 (m, 2 H), 2.09 (dt, J = 5.1, 2.9 Hz, 1 H), 1.88 (tdd, J = 11.2, 5.1, 2.5 Hz, 1 H), 1.47 (tt, J = 10.2, 3.7 Hz, 1 H); ^{13}C NMR (126 MHz, MeOH-d_4) 168.2, 151.4, 151.1, 148.8, 147.4, 144.5, 138.6, 131.3, 131.2, 131.1, 130.4, 129.2, 126.1, 124.3, 122.9, 121.3, 117.6, 113.5, 69.7, 66.4, 62.5, 59.2, 53.7, 39.2, 27.7, 26.0, 22.6, 14.4; LRMS (ES$^+$) 111.3 (71), 133.1 (8), 157.1 (7), 179.1 (25), 315.9 (4), 474.4 (100), 476.4 (40), 477.4 (15), 478.6 (2); HRMS (ESI, [M]$^+$) calcd for $C_{28}H_{29}N_3O_2Cl^+$ 474.1948, found 474.1946.



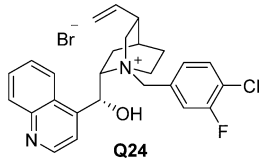
Q22

Data for ***Q22****:* ^{1}H NMR (500 MHz, MeOH-d_4) 8.95 (d, J = 4.6 Hz, 1 H), 8.30 (dd, J = 8.4, 1.3 Hz, 1 H), 8.13 (d, J = 8.4 Hz, 1 H), 7.96 (d, J = 4.6 Hz, 1 H), 7.91−7.78 (m, 4 H), 7.73 (d, J = 7.7 Hz, 1 H), 7.67 (dd, J = 7.8, 1.6 Hz, 1 H), 7.35 (s, 1 H), 7.21 (d, J = 7.3 Hz, 1 H), 6.69 (br s, 1 H), 5.71 (ddd, J = 17.2, 10.5, 6.8 Hz, 1 H), 5.24 (d, J = 12.4 Hz, 1 H), 5.16 (dt, J = 17.2, 1.1 Hz, 1 H), 5.08 (d, J = 12.4 Hz, 1 H), 5.01 (dd, J = 10.5, 1.3 Hz, 1 H), 4.50 (tdd, J = 11.3, 5.2, 2.7 Hz, 1 H), 4.02 (br t, J = 9.3 Hz, 1 H), 3.71 (br d, J = 12.2 Hz, 1 H), 3.56 (dd, J = 12.8, 10.6 Hz, 1 H), 3.47 (td, J = 11.1, 4.0 Hz, 1 H), 2.78−2.69 (m, 1 H), 2.71 (t, J = 7.8 Hz, 2 H), 2.34−2.21 (m, 2 H), 2.08 (q, J = 3.1 Hz, 1 H), 1.96−1.85 (m, 1 H), 1.66 (tt, J = 7.8, 6.6 Hz, 2 H), 1.53 (s, 3 H), 1.48 (s, 3 H), 1.42 (dt, J = 14.9, 7.4 Hz, 3 H), 0.97 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (126 MHz, MeOH-d_4) 156.0, 155.7, 151.1, 148.8, 147.6, 144.9, 143.2, 138.8, 136.8, 133.9, 131.2, 130.4, 129.2, 128.7, 126.6, 126.2, 126.2, 124.1, 123.9, 121.5, 121.3, 121.3, 117.5, 69.5, 66.3, 65.7, 62.0, 52.8, 48.0, 39.2, 37.0. 35.2, 28.1, 27.4, 27.4, 27.2, 26.0, 23.5, 22.5, 14.3; LRMS (ES$^+$) 111.3 (70), 133.1 (12), 157.2 (20), 179.1 (38), 279.4 (4), 318.5 (4), 357.5 (6), 501.5 (2), 557.6 (100), 558.6 (40), 559.7 (12), 560.6 (2); HRMS (ESI, [M]$^+$) calcd for $C_{39}H_{45}N_2O^+$ 557.3532, found 557.3527.



Q23

Data for ***Q23****:* ^{1}H NMR (500 MHz, MeOH-d_4) 8.95 (d, J = 4.6 Hz, 1 H), 8.30 (d, J = 8.3 Hz, 1 H), 8.14 (d, J = 9.1 Hz, 1 H), 7.98 (t, J = 1.8 Hz, 1 H), 7.95 (d, J = 4.6 Hz, 1 H), 7.90−7.84 (m, 2 H), 7.81 (ddd, J = 8.3, 6.8, 1.4 Hz, 1 H), 7.73−7.64 (m, 4 H), 7.48 (t, J = 7.7 Hz, 2 H), 7.39 (t, J = 7.4 Hz, 1 H), 6.68 (br s, 1 H), 5.70 (ddd, J = 17.2, 10.5, 6.7 Hz, 1 H), 5.25 (d, J = 12.4 Hz, 1 H), 5.15 (d, J = 17.2 Hz, 1 H), 5.09 (d, J = 12.4 Hz, 1 H), 5.00 (d, J = 10.5 Hz, 1 H), 4.54−4.45 (m, 1 H), 4.03 (t, J = 9.1 Hz, 1 H), 3.69 (ddd, J = 12.8, 5.1, 3.0 Hz, 1 H), 3.57 (dd, J = 12.8, 10.6 Hz, 1 H), 3.49 (td, J = 12.0, 4.6 Hz, 1 H), 2.78−2.70 (m, 1 H), 2.35−2.21 (m, 2 H), 2.09 (dt, J = 5.5, 3.3 Hz, 1 H), 1.90 (ddt, J = 17.8, 11.3, 2.7 Hz, 1 H), 1.46 (dtt, J = 13.6, 6.9, 2.9 Hz, 1 H); ^{13}C NMR (126 MHz, MeOH-d_4) 151.0, 148.8, 147.5, 143.7, 141.1, 138.7, 133.6, 133.4, 131.2, 130.9, 130.4, 130.2, 130.1, 129.3, 129.2, 129.0, 128.2, 1226.2, 124.1, 121.3, 117.5, 69.7, 66.3, 65.2, 52.9, 39.2, 28.0, 26.0, 22.5; LRMS (ES$^+$) 111.2 (2), 231.3 (4), 461.4 (100), 462.5 (40), 463.5 (12), 464.4 (4). HRMS (ESI, [M]$^+$) calcd for $C_{32}H_{33}N_2O^+$ 461.2593, found 461.2590.



Q24

Data for ***Q24****:* ^{1}H NMR (400 MHz, MeOH-d_4) 8.95 (d, J = 4.6 Hz, 1 H), 8.31 (d, J = 8.2 Hz, 1 H), 8.12 (d, J = 8.2 Hz, 1 H), 7.97 (d, J = 5.8 Hz, 1 H), 7.90−7.71 (m, 3 H), 7.46 (t, J = 8.7 Hz, 1 H), 6.62 (br s, 1 H), 5.68 (ddd, J = 17.2, 10.6, 6.8 Hz, 1 H), 5.19 (d, J = 12.3 Hz, 1 H), 5.17 (d, J = 17.0 Hz, 1 H), 5.08 (d, J = 12.5 Hz, 1 H), 5.00 (d, J = 10.4 Hz, 1 H), 4.53−4.40 (m, 1 H), 4.00 (t, J = 8.9 Hz, 1 H), 3.69 (br d, J = 13.2 Hz, 1 H), 3.48 (t, J = 11.6 Hz, 1 H), 3.40 (td, J = 11.4, 4.4 Hz, 1 H), 2.79−2.65 (m, 1 H), 2.34−2.17 (m, 2 H), 2.12−2.04 (m, 1 H), 1.89 (br t, J = 10.9 Hz, 1 H), 1.40 (t, J = 11.4 Hz, 1 H); ^{13}C NMR (126 MHz, MeOH-d_4) 160.7 (d, J_{C-F} = 252.4 Hz), 151.0, 148.7, 147.4, 138.6, 137.2, 135.6 (d, J_{C-F} = 8.0 Hz), 131.1, 130.3, 129.2, 126.4 (d, J_{C-F} = 4.1 Hz), 126.0, 124.2, 122.8 (d, J_{C-F} = 18.1 Hz), 121.3, 118.5 (d, J_{C-F} = 21.7 Hz), 117.6, 69.8, 66.3, 63.5, 61.8, 52.7, 39.1, 28.0, 25.9, 22.5; ^{19}F NMR (470 MHz, MeOH-d_4) −115.0 (br q, J = 7.2 Hz); LRMS (ES$^+$) 111.3 (15), 219.2 (2), 235.4 (2), 437.3 (100), 439.4 (63), 440.4 (18), 441.5 (2); HRMS (ESI, [M]$^+$) calcd for $C_{26}H_{27}N_2OFCl^+$ 437.1796, found 437.1794.

DOI: 10.1021/acs.joc.5b01759
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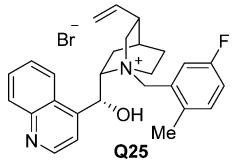
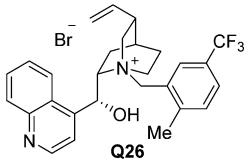


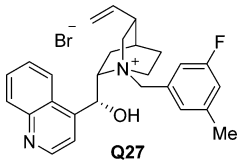
Q25

Data for ***Q25****:* ^{1}H NMR (500 MHz, MeOH-d_4) 8.96 (d, J = 4.5 Hz, 1 H), 8.33 (dd, J = 8.4, 1.4 Hz, 1 H), 8.13 (dd, J = 8.4, 1.4 Hz, 1 H), 7.97 (d, J = 4.6 Hz), 7.87 (ddd, J = 8.4, 6.9, 1.4 Hz), 7.81 (ddd, J = 8.2, 6.8, 1.4 Hz, 1 H), 7.56 (dd, J = 9.5, 2.8 Hz, 1 H), 7.47 (ddd, J = 8.7, 5.8 Hz, 1 H), 7.25 (td, J = 8.3, 2.7 Hz, 1 H), 6.69 (br d, J = 2.6 Hz, 1 H), 5.69 (ddd, J = 17.2, 10.5, 6.6 Hz, 1 H), 5.37 (d, J = 12.8 Hz, 1 H), 5.18 (dd, J = 17.2, 1.2 Hz, 1 H), 5.00 (d, J = 10.5 Hz, 1 H), 4.98 (d, J = 12.6 Hz, 1 H), 4.55 (tdd, J = 11.2, 5.8, 3.0 Hz, 1 H), 4.08 (td, J = 8.9, 8.4, 2.1 Hz, 1 H), 3.79 (ddd, J = 12.6, 4.6, 3.1 Hz, 1 H), 3.62 (dd, J = 12.5, 10.5 Hz, 1 H), 3.24 (tdd, J = 11.3, 4.4, 1.7 Hz, 1 H), 2.80−2.71 (m, 1 H), 2.56 (s, 3 H), 2.30−2.17 (m, 2 H), 2.08 (q, J = 3.3 Hz, 1 H), 1.86 (tdd, J = 10.9, 5.7, 3.0 Hz, 1 H), 1.36 (dddd, J = 13.3, 10.5, 5.1, 2.8 Hz, 1 H); ^{13}C NMR (126 MHz, MeOH-d_4) 162.2 (d, J_{C-F} = 244.7 Hz), 151.0, 148.7, 147.5, 138.7, 137.7 (d, J_{C-F} = 3.3 Hz), 134.7 (d, J_{C-F} = 7.8 Hz), 131.2, 130.3, 129.2, 129.1 (d, J_{C-F} = 7.3 Hz), 126.1, 124.1, 122.2 (d, J_{C-F} = 22.3 Hz), 121.3, 118.8 (d, J_{C-F} = 20.9 Hz), 117.5, 69.4, 66.6, 62.1, 61.7, 52.6, 39.2, 27.6, 26.0, 22.7, 19.9; ^{19}F NMR (470 MHz, MeOH-d_4) −118.2 (q, J = 8.0 Hz); LRMS (ES$^+$) 111.3 (2), 417.4 (100), 418.4 (45), 419.4 (15), 420.4 (2); HRMS (ESI, [M]$^+$) calcd for $C_{27}H_{30}N_2OF^+$ 417.2342, found 417.2335.



Q26

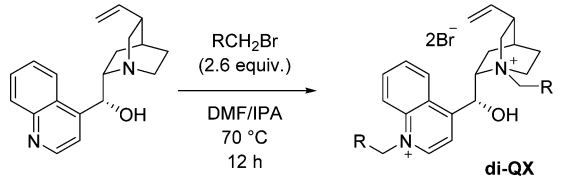
Data for ***Q26****:* ^{1}H NMR (400 MHz, MeOH-d_4) 8.94 (d, J = 4.6 Hz, 1 H), 8.33−8.25 (m, 1 H), 8.11 (dd, J = 8.4, 1.7 Hz, 1 H), 7.95 (d, J = 4.6 Hz), 7.88−7.82 (m, 1 H), 7.82−7.74 (m, 2 H), 7.67 (d, J = 8.1 Hz, 1 H), 6.69 (br s, 1 H), 5.66 (ddd, J = 17.2, 10.5, 6.7 Hz, 1 H), 5.44 (d, J = 13.0 Hz, 1 H), 5.15 (d, J = 17.2 Hz, 1 H), 5.06−4.95 (m, 2 H), 4.55 (dt, J = 11.6, 7.9 Hz, 1 H), 4.07 (br t, J = 9.2 Hz, 1 H), 3.84−3.73 (m, 1 H), 3.54 (dd, J = 12.4, 10.5 Hz, 1 H), 3.34−3.27 (m, 1 H), 3.19 (td, J = 11.4, 4.3 Hz, 1 H), 2.77−2.68 (m, 1 H), 2.66 (s, 3 H), 2.32−2.14 (m, 1 H), 2.08−2.03 (m, 2 H), 1.90−1.78 (m, 1 H), 1.35 (br t, J = 11.7 Hz, 1 H); ^{13}C NMR (126 MHz, MeOH-d_4) 151.0, 148.7, 147.4, 146.7, 138.7, 134.1, 132.6 (q, J_{C-F} = 3.7 Hz), 131.2, 130.4, 130.0 (d, J_{C-F} = 31.5 Hz), 129.2, 128.5, 128.4 (q, J_{C-F} = 4.1 Hz), 126.1, 124.0, 121.3, 117.6, 69.6, 66.6, 62.0, 61.5, 52.7, 39.3, 27.7, 26.0, 22.7, 20.8; ^{19}F NMR (470 MHz, MeOH-d_4) −64.3 (s, 3F); LRMS (ES$^+$) 111.4 (2), 234.4 (3), 467.4 (100), 468.5 (50), 469.5 (20), 470.4 (3); HRMS (ESI, [M − 1]$^+$) calcd for $C_{28}H_{30}N_2OF_3^+$ 467.2310, found 467.2306.



Q27

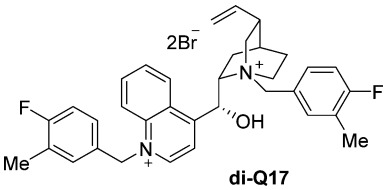
Data for ***Q27****:* ^{1}H NMR (500 MHz, MeOH-d_4) 8.95 (d, J = 4.5 Hz, 1 H), 8.27 (dd, J = 8.4, 1.4 Hz, 1 H), 8.13 (dd, J = 8.5, 1.4 Hz, 1 H), 7.95 (dd, J = 4.6, 0.9 Hz, 1 H), 7.91−7.83 (m, 1 H), 7.80 (td, J = 7.6, 7.0, 1.2 Hz, 1 H), 7.38 (s, 1 H), 7.38 (dt, J = 9.2, 2.1 Hz, 1 H), 7.18 (dt, J = 9.2, 1.7 Hz, 1 H), 6.62 (br s, 1 H), 5.69 (ddd, J = 17.2, 10.5, 6.7 Hz, 1 H), 5.18−5.12 (m, 2 H), 5.01 (d, J = 10.5 Hz, 1 H), 4.96 (d, J = 12.4 Hz, 1 H), 4.50−4.41 (m, 1 H), 3.97 (tt, J = 8.4, 2.2 Hz, 1 H), 3.63 (ddd, J = 12.7, 5.0, 3.1 Hz, 1 H), 3.51 (dd, J = 12.7, 10.5 Hz, 1 H), 3.47−3.39 (m, 1 H), 2.78−2.69 (m, 1 H), 2.46 (s, 3 H), 2.32−2.20 (m, 2 H), 2.08 (br q, J = 3.4 Hz, 1 H), 1.94−1.86 (m, 1 H), 1.42 (ddd, J = 13.6, 8.2, 5.0 Hz, 1 H); ^{13}C NMR (126 MHz, MeOH-d_4) 164.2 (d, J_{C-F} = 246.3 Hz), 151.0, 148.7, 147.6, 143.3 (d, J_{C-F} = 8.2 Hz), 138.7, 131.6 (d, J_{C-F} = 2.7 Hz), 131.2, 130.6 (d, J_{C-F} = 8.3 Hz), 130.3, 129.2, 126.1, 124.2, 121.3, 119.1 (d, J_{C-F} = 21.2 Hz), 118.6 (d, J_{C-F} = 22.6 Hz), 117.5, 69.8, 66.3, 64.4, 62.1, 52.9, 39.1, 27.9, 25.9, 22.5, 21.3; ^{19}F NMR (470 MHz, MeOH-d_4) −114.8 (t, J = 8.7 Hz); LRMS (ES$^+$) 295.3 (20), 417.2 (100), 418.4 (73), 419.4 (25), 420.4 (4); HRMS (ESI, [M]$^+$) calcd for $C_{27}H_{30}N_2OF^+$ 417.2342, found 417.2336.

6.6. General Procedure for the Preparation of Bis-quaternized Phase-Transfer Catalysts.



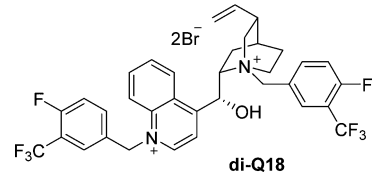
di-QX

To a 10-mL Schlenk flask fitted with a stir bar and septum were added cinchonidine (100 mg, 0.34 mmol, 1.0 equiv), DMF (0.41 mL, 0.83 M), alkylating agent (2.6 equiv), and isopropyl alcohol (0.06 mL, 5.9 M). The reaction flask was stirred at rt and then heated to 70 °C in an oil bath for 12 h. After 12 h, the reaction was allowed to cool to rt for 1 h, and then EtOAc (4.6 mL) was added to precipitate the salt. If precipitation did not occur, hexanes were added dropwise until a heterogeneous reaction mixture resulted. This solution was allowed to cool in an ice−water bath for 2 h, and then the precipitated salt was collected by Büchner filtration and washed with an excess of ice-cold EtOAc and room temperature hexanes. The powder was dried in air on the filter paper for 30 min and then collected into a tared scintillation vial. The powder was placed under high vacuum (0.1 mmHg) and stirred at rt for 24 h in order to remove residual DMF. The salts were used without further purification.



di-Q17

Data for ***di-Q17****:* ^{1}H NMR (500 MHz, MeOH-d_4) 9.54 (d, J = 6.2 Hz, 1 H), 8.78 (dd, J = 8.6, 1.5 Hz, 1 H), 8.63 (d, J = 9.0 Hz, 1 H), 8.58 (d, J = 6.1 Hz, 1 H), 8.30−8.26 (m, 1 H), 8.22−8.17 (m, 1 H), 7.71 (br d, J = 7.0 Hz, 1 H), 7.63 (ddd, J = 7.8, 4.8, 2.3 Hz, 1 H), 7.41 (br d, J = 5.6 Hz, 1 H), 7.29 (ddd, J = 7.9, 4.6, 2.4 Hz, 1 H), 7.24 (t, J = 8.9 Hz, 1 H), 7.11 (t, J = 9.0 Hz, 1 H), 6.90 (br s, 1 H), 6.31 (q, J = 8.3 Hz, 2 H), 5.74 (ddd, J = 18.3, 10.4, 7.0 Hz, 1 H), 5.23−5.14 (m, 3 H), 5.00 (dd, J = 10.4, 1.3 Hz, 1 H), 4.41 (tdd, J = 11.5, 5.2, 3.0 Hz, 1 H), 4.15 (t, J = 9.2 Hz, 1 H), 3.79 (dt, J = 13.3, 3.8 Hz, 1 H), 3.49 (dd, J = 10.7, 12.8 Hz, 1 H), 3.43 (dt, J = 11.9, 5.8 Hz, 1 H), 2.78−2.71 (m, 1 H), 2.37 (s, 3 H), 2.24 (s, 3 H), 2.29−2.22 (m, 2 H), 2.10 (dt, J = 5.4, 2.9 Hz, 1 H), 1.91 (td, J = 13.4, 11.0, 5.4, 1 H), 1.59 (ddt, J = 13.7, 10.4, 3.4 Hz, 1 H); ^{13}C NMR (126 MHz, d_6-MeOH) 161.7 (J_{C-F} = 247.1 Hz), 160.7 (J_{C-F} = 244.9), 158.0, 149.4, 138.1, 137.1, 137.1, 135.3, 133.5 (J_{C-F} = 8.5 Hz), 131.2, 130.6, 129.5 (J_{C-F} = 8.5 Hz), 127.5 (J_{C-F} = 8.5 Hz), 126.8, 126.1, 125.2 (J_{C-F} = 17.6 Hz), 124.9 (J_{C-F} = 17.3 Hz), 123.8 (J_{C-F} = 3.5 Hz), 121.6, 119.9, 116.6, 115.6 (J_{C-F} = 22.6 Hz), 115.5 (J_{C-F} = 22.5 Hz), 67.1, 64.7, 61.6, 59.3, 59.2, 50.5, 36.9, 26.0, 24.2, 21.2, 14.2 (J_{C-F} = 3.6 Hz), 14.2 (J_{C-F} = 3.6 Hz); ^{19}F NMR (470 MHz, MeOH-d_4) −116.0 (br s), −117.5 (br s); LRMS (ES$^+$) 270.4 (100), 417.4 (40), 418.4 (12), 419.2 (5); HRMS (ESI, [M − 1]$^+$) calcd for $C_{35}H_{37}N_2OF_2^+$ 539.2874, found 539.2868.



di-Q18

Data for ***di-Q18****:* ^{1}H NMR (400 MHz, MeOH-d_4) 9.60 (d, J = 6.2 Hz, 1 H), 8.83 (d, J = 8.5 Hz, 1 H), 8.61 (d, J = 7.0 Hz, 1H), 8.31 (ddd, J = 8.8, 6.1, 1.3 Hz, 1 H), 8.26−8.14 (m, 3 H), 7.91 (dd, J = 6.7, 2.3 Hz, 1 H), 7.73 (ddd, J = 7.6, 4.5, 2.4 Hz, 1 H), 7.59 (d, J = 9.4 Hz, 1 H), 7.43 (t, J = 9.4 Hz, 1 H), 6.92 (br s, 1 H), 6.48 (d, J = 15.6 Hz, 1

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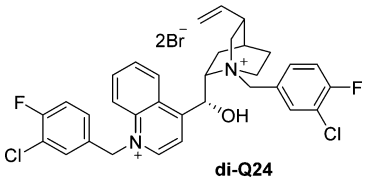
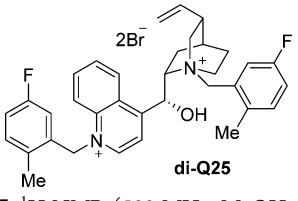
H), 6.43 (d, J = 16.0 Hz, 1 H), 5.75 (ddd, J = 17.4, 10.5, 6.9 Hz, 1 H), 5.36 (d, J = 12.4 Hz, 1 H), 5.29 (d, J = 12.4 Hz, 1 H), 5.21 (dt, J = 17.1, 1.2 Hz, 1 H), 5.00 (dt, J = 10.6, 1.1 Hz, 1 H), 4.49 (tdd, J = 11.5, 6.1, 3.1 Hz, 1 H), 4.18 (t, J = 9.3 Hz, 1 H), 3.87 (dt, J = 12.6, 3.9 Hz, 1 H), 3.48 (dd, J = 11.7, 5.1 Hz, 1 H), 2.80−2.71 (m, 1 H), 2.33−2.20 (m, 2 H), 2.14−2.08 (m, 1 H), 1.97−1.86 (m, 1 H), 1.61 (ddd, J = 15.8, 8.5, 4.6 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 159.9 (J_{C-F} = 257.7 Hz), 158.9 (J_{C-F} = 255.4 Hz), 158.1, 149.7, 141.0 (J_{C-F} = 9.4 Hz), 138.0, 137.1, 135.5, 135.0 (J_{C-F} = 9.2 Hz), 132.7 (J_{C-F} = 4.2 Hz), 130.7, 130.6 (J_{C-F} = 3.6 Hz), 127.6 (J_{C-F} = 5.0 Hz), 126.9, 126.1, 125.2 (J_{C-F} = 3.7 Hz), 123.5 (J_{C-F} = 10.1 Hz), 121.7, 121.3 (J_{C-F} = 10.3 Hz), 119.8, 118.0 (J_{C-F} = 20.8 Hz), 117.9 (J_{C-F} = 20.6 Hz), 117.2 (J_{C-F} = 12.5 Hz), 116.9 (J_{C-F} = 12.6 Hz), 116.6, 67.4, 64.7, 60.5, 59.0, 58.5, 50.5, 36.9, 26.0, 24.3, 21.2; ^{19}F NMR (470 MHz, MeOH-d_4) −60.4 (CF_3, d, J = 13.0 Hz), −60.5 (CF_3, d, J = 11.6 Hz), −116.0 (Ar-F, ddd, J = 5.8 Hz, 13.0, 18.8 Hz), −114.4 (Ar-F, ddt, J = 6.5, 11.6, 17.3 Hz); LRMS (ES$^+$) 111.3 (2), 315.4 (2), 324.4 (100), 360.9 (2), 471.4 (12), 472.4 (3).



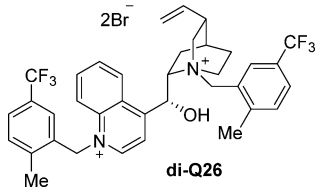
di-Q24

Data for ***di-Q24****:* ^{1}H NMR (500 MHz, MeOH-d_4) 9.57 (d, J = 6.2 Hz, 1 H), 8.80 (dd, J = 8.7, 1.3 Hz, 1 H), 8.59 (d, J = 7.1 Hz, 2 H), 8.30 (ddd, J = 8.8, 7.0, 1.0 Hz, 1 H), 8.21 (ddd, J = 8.2, 7.0, 1.0 Hz, 1 H), 8.02 (dd, J = 6.0, 2.3 Hz, 1 H), 7.80 (ddd, J = 8.5, 4.5, 2.3 Hz, 1 H), 7.67 (dd, J = 6.8, 2.3 Hz, 1 H), 7.47 (t, J = 8.7 Hz, 1 H), 7.42 (ddd, J = 8.7, 4.4, 2.3 Hz, 1 H), 7.34 (t, J = 8.8 Hz, 1 H), 6.89 (br s, 1 H), 6.39 (d, J = 15.6 Hz, 1 H), 6.34 (d, J = 15.6 Hz, 1 H), 5.74 (ddd, J = 17.3, 10.5, 6.9 Hz, 1 H), 5.25 (d, J = 12.5 Hz, 1 H), 5.21 (d, J = 17.3 Hz, 1 H), 5.20 (d, J = 12.4 Hz, 1 H), 5.01 (dt, J = 10.5, 1.0 Hz, 1 H), 4.44 (tdd, J = 11.2, 5.0, 2.7 Hz, 1 H), 4.16 (t, J = 9.2 Hz, 1 H), 3.82 (ddd, J = 12.7, 4.8, 3.3 Hz, 1 H), 3.50 (dd, J = 12.7, 10.7 Hz, 1 H), 3.43 (td, J = 11.5, 11.0, 4.3 Hz, 1 H), 2.80−2.72 (m, 1 H), 2.32−2.21 (m, 2 H), 1.93 (dt, J = 7.6, 6.9, 4.7, 3.4, 2.2 Hz, 1 H), 1.61 (dq, J = 10.2, 3.4, 3.2 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 158.3 (J_{C-F} = 250.3 Hz), 158.1, 157.3 (J_{C-F} = 248.6 Hz), 149.7, 138.1, 137.1, 135.8, 134.9 (J_{C-F} = 8.0 Hz), 131.3 (J_{C-F} = 3.8 Hz), 130.7, 130.5, 128.9 (J_{C-F} = 7.7 Hz), 126.8, 126.1, 125.9 (J_{C-F} = 3.9 Hz), 121.7, 120.1 (J_{C-F} = 27.1 Hz), 120.0 (J_{C-F} = 27.1 Hz), 119.8, 117.6 (J_{C-F} = 21.4 Hz), 117.4 (J_{C-F} = 21.4 Hz), 116.6, 67.3, 64.7, 60.7, 59.2, 58.6, 50.6, 36.9, 25.9, 24.3, 21.2; ^{19}F NMR (470 MHz, MeOH-d_4) −114.7 (q, J = 9.7 Hz), −116.2 (q, J = 8.2 Hz); LRMS (ES$^+$) 111.3 (20), 157.1 (2), 290.3 (100), 218.1 (92), 329.4 (30), 330.0 (25), 330.4 (21), 437.3 (3); HRMS (ESI, [M − 1]$^+$) calcd for $C_{33}H_{31}N_2OF_2Cl_2^+$ 579.1782, found 579.1770.



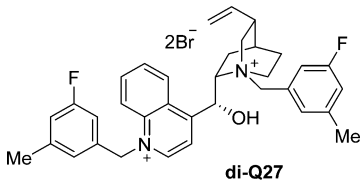
di-Q25

Data for ***di-Q25****:* ^{1}H NMR (500 MHz, MeOH-d_4) 9.36 (d, J = 6.2 Hz, 1 H), 8.88 (d, J = 8.4 Hz, 1 H), 8.59 (d, J = 6.2 Hz, 1 H), 8.30 (ddd, J = 8.8, 7.0, 1.3 Hz, 1 H), 8.24 (ddd, J = 8.2, 7.0, 1.2 Hz, 1 H), 7.63 (dd, J = 9.6, 2.9 Hz, 1 H), 7.46 (ddd, J = 13.8, 8.5, 5.7 Hz, 1 H), 7.26 (td, J = 8.5, 2.8 Hz, 1 H), 7.11 (td, J = 9.5, 2.8 Hz, 1 H), 7.01 (d, J = 2.5 Hz, 1 H), 6.51 (dd, J = 9.5, 2.7 Hz), 6.41 (d, J = 16.2 Hz, 1 H), 6.33 (d, J = 16.2 Hz, 1 H), 5.77 (ddd, J = 17.2, 10.5, 6.8 Hz, 1 H), 5.37 (d, J = 12.7 Hz, 1 H), 5.24 (d, J = 17.2 Hz, 1 H), 5.18 (d, J = 12.8 Hz, 1 H), 5.02 (dt, J = 10.6, 1.2 Hz, 1 H), 4.58−4.47 (m, 1 H), 4.26 (br t, J = 9.3 Hz, 1 H), 3.94 (dt, J = 12.4, 3.8 Hz, 1 H), 3.65 (t, J = 11.5 Hz, 1 H), 3.31−3.23 (m, 1 H), 2.83−2.72 (m, 1 H), 2.58 (s, 3 H), 2.47 (s, 3 H), 2.33−2.18 (m, 2 H), 2.15−2.07 (m, 1 H), 1.95−1.83 (m, 1 H), 1.65−1.53 (m, 1 H); ^{13}C NMR (126 MHz, *d6*-DMSO) 160.7 (J_{C-F} = 242.0 Hz), 160.0 (J_{C-F} = 242.3 Hz), 158.4, 149.3, 138.1, 137.6, 136.6, 135.6, 133.9 (J_{C-F} = 7.3 Hz), 133.3 (J_{C-F} = 7.9 Hz), 132.6 (J_{C-F} = 8.0 Hz), 132.3 (J_{C-F} = 3.1 Hz), 130.7, 128.3, 126.8, 121.8, 121.2 (J_{C-F} = 21.8 Hz), 119.9, 117.3 (J_{C-F} = 20.5 Hz), 116.6, 115.2 (J_{C-F} = 20.8 Hz), 113.4 (J_{C-F} = 23.4 Hz), 67.0, 65.1, 59.6, 59.4, 58.1, 50.9, 27.1, 25.7, 24.5, 21.3, 18.5, 18.1; ^{19}F NMR (470 MHz, MeOH-d_4) −116.5 (q, J = 9.5 Hz), −117.2 (q, J = 9.5 Hz); LRMS (ES$^+$) 111.3 (2), 209.4 (3), 270.4 (100), 285.4 (2), 417.4 (7), 418.4 (3); HRMS (ESI, [M − 1]$^+$) calcd for $C_{35}H_{37}N_2OF_2^+$ 539.2874, found 539.2868.



di-Q26

Data for ***di-Q26****:* ^{1}H NMR (500 MHz, MeOH-d_4) 9.35 (d, J = 6.2 Hz, 1 H), 8.91 (dd. J = 8.6, 1.5 Hz, 1 H), 8.61 (d, J = 6.2 Hz, 1 H), 8.52 (d, J = 8.9 Hz, 1 H), 8.38−8.22 (m, 2 H), 8.17 (d, J = 2.0 Hz, 1 H), 7.79 (br d, J = 8.1 Hz, 1 H), 7.72−7.62 (m, 3 H), 7.06 (d, J = 2.7 Hz, 1 H), 6.97 (d, J = 1.8 Hz, 1 H), 6.48 (q, J = 6.7 Hz, 2 H), 5.76 (ddd, J = 17.1, 10.6, 6.6 Hz, 1 H), 5.47 (d, J = 13.0 Hz, 1 H), 5.29 (d, J = 12.9 Hz, 1 H), 5.23 (d, J = 17.1 Hz, 1 H), 5.01 (dd, J = 10.6, 1.5 Hz, 1 H), 4.63−4.50 (m, 1 H), 4.29 (t, J = 9.2 Hz, 1 H), 3.99 (tt, J = 14.9, 3.9 Hz, 1 H), 3.59 (dd, J = 12.4, 10.4 Hz, 1 H), 3.30−3.19 (m, 1 H), 2.82−2.74 (m, 1 H), 2.70 (s, 3 H), 2.59 (s, 3 H), 2.26 (dt, J = 10.4, 15.8 Hz, 2 H), 2.14−2.08 (m, 1 H), 1.95−1.84 (m, 1 H), 1.58−1.47 (m, 1 H); ^{13}C NMR (126 MHz, *d6*-DMSO) 158.3, 149.2, 145.6, 142.0, 138.1, 138.0, 137.5, 135.7, 132.8, 132.7, 131.9, 131.5, 130.8, 127.7, 127.6, 127.3, 127.1, 127.0, 126.8, 125.8, 125.6, 125.2, 124.6, 123.3, 123.2, 123.0, 122.8, 121.7, 120.5, 119.9, 116.5, 67.3, 66.9, 65.1, 64.7, 59.4, 59.1, 59.0, 57.8, 54.9, 50.9, 50.8, 37.1, 36.9, 34.2, 25.6, 24.4, 21.2, 21.2, 20.3, 20.2, 19.0; HRMS (ESI, [M − 1]$^+$) calcd for $C_{37}H_{37}N_2OF_6^+$ 639.2810, found 639.2795.



di-Q27

Data for ***di-Q27****:* ^{1}H NMR (500 MHz, MeOH-d_4) 9.58 (d, J = 6.2 Hz, 1 H), 8.77 (d, J = 8.0 Hz, 1 H), 8.60 (d, J = 6.2 Hz, 1 H), 8.57 (d, J = 8.9 Hz, 1 H), 8.28 (ddd, J = 8.8, 7.1, 1.3 Hz, 1 H), 8.20 (J = 8.3, 7.1, 1.0 Hz, 1 H), 7.45 (br s, 1 H), 7.39 (dt, J = 9.2, 2.0 Hz, 1 H), 7.19 (dt, J = 9.8, 1.7 Hz, 1 H), 7.09 (br s, 1 H), 7.01 (br d, J = 9.5 Hz, 1 H), 6.95 (dt, J = 9.3, 2.1 Hz, 1 H), 6.90 (br s, 1 H), 6.34 (q, J = 9.1 Hz, 2 H), 5.74 (ddd, J = 17.3, 10.5, 6.9 Hz, 1 H), 5.23−5.13 (m, 3 H), 5.01 (dt, J = 10.6, 1.1 Hz, 1 H), 4.49−4.39 (m, 1 H), 4.14 (dd, J = 10.4, 8.1 Hz, 1 H), 3.78 (ddd, J = 12.7, 5.0, 3.2 Hz, 1 H), 3.52 (dd, J = 12.8, 10.7 Hz, 1 H), 3.50−3.43 (m, 1 H), 2.79−2.72 (m, 1 H), 2.48 (s, 3 H), 2.35 (s, 3 H), 2.31−2.22 (m, 2 H), 2.11 (dq, J = 6.6, 3.5, 3.1 Hz, 1 H), 1.97−1.88 (m, 1 H), 1.60 (ddt, J = 13.6, 10.2, 3.5 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 162.2 (J_{C-F} = 244.2 Hz), 161.8 (J_{C-F} = 244.1 Hz), 158..1, 149.8, 141.5 (J_{C-F} = 8.3 Hz), 141.0 (J_{C-F} = 8.2 Hz), 138.1, 137.1, 135.9 (J_{C-F} = 8.4 Hz), 135.4, 130.7, 130.6, 129.9 (J_{C-F} = 8.5 Hz), 126.6, 126.1, 124.2 (J_{C-F} = 2.5 Hz), 121.7, 119.8, 117.6 (J_{C-F} = 5.6 Hz), 117.5 (J_{C-F} = 4.4 Hz), 116.6, 116.2 (J_{C-F} = 20.9 Hz), 111.8 (J_{C-F} = 22.8 Hz), 67.2, 64.7, 61.5, 59.5, 59.4, 50.8, 36.8, 25.9, 24.2, 21.3, 20.8, 20.8; ^{19}F NMR (470 MHz, MeOH-d_4) −113.3 (t, J = 10.6 Hz), −113.8 (t, J = 10.0 Hz); LRMS (ES$^+$) 111.3 (23), 179.1 (10), 270.4 (100), 309.4 (53), 310.0 (21), 417.4 (5); HRMS (ESI, [M − 1]$^+$) calcd for $C_{35}H_{37}N_2OF_2^+$ 539.2874, found 539.2864.

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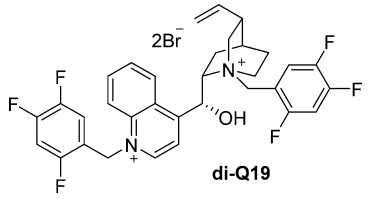
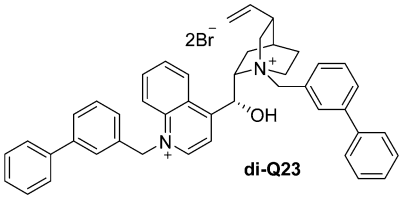


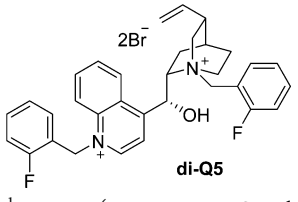
di-Q19

Data for ***di-Q19:*** ^{1}H NMR (400 MHz, MeOH-d_4) 9.59 (dd, J = 6.3, 1.5 Hz, 1 H), 8.84 (d, J = 9.0 Hz, 1 H), 8.61 (d, J = 9.2 Hz, 1 H), 8.59 (d, J = 6.5 Hz, 1 H), 8.34 (ddd, J = 8.8, 7.1, 1.3 Hz, 1 H), 8.23 (dd, J = 8.1, 6.9 Hz, 1 H), 8.07−7.99 (m, 1 H), 7.60 (dt, J = 10.4, 8.0 Hz, 1 H), 7.51 (td, J = 10.0, 6.6 Hz, 1 H), 7.41 (td, J = 10.2, 6.5 Hz, 1 H), 6.91 (br s, 1 H), 6.43 (d, J = 16.2 Hz, 1 H), 6.38 (d, J = 16.2 Hz, 1 H), 5.74 (ddd, J = 17.3, 10.5, 6.9 Hz, 1 H), 5.29 (d, J = 12.9 Hz, 1 H), 5.22 (d, J = 13.0 Hz, 1 H), 5.22 (d, J = 17.0 Hz, 1 H), 5.01 (td, J = 10.4, 1.2 Hz, 1 H), 4.54−4.41 (m, 1 H), 4.20 (br t, J = 9.3 Hz, 1 H), 3.88 (dt, J = 12.9, 3.9 Hz, 1 H), 3.63 (t, J = 11.5 Hz, 1 H), 3.43−3.32 (m, 1 H), 2.83−2.73 (m, 1 H), 2.32−2.20 (m, 2 H), 2.16−2.08 (m, 1 H), 1.98−1.88 (m, 1 H), 1.62−1.51 (m, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 158.8, 157.7 (J_{C-F} = 248.4, 10.2, 1.8 Hz), 156.0 (J_{C-F} = 247.0, 10.4, 1.8 Hz), 151.0 (J_{C-F} = 252.1, 15.0, 14.4 Hz), 149.9, 149.7 (J_{C-F} = 251.3, 13.0 Hz), 146.1 (J_{C-F} = 253.9 Hz), 146.1 (J_{C-F} = 253.9 Hz), 138.0, 137.2, 135.6, 130.7, 127.0, 126.1, 123.4 (J_{C-F} = 18.2, 2.5 Hz), 121.5, 119.5, 119.0 (J_{C-F} = 20.5, 4.4 Hz), 117.5 (J_{C-F} = 15.0, 6.0 5.4 Hz), 116.7, 112.3 (J_{C-F} = 15.6, 6.2, 4.0 Hz), 107.2 (J_{C-F} = 21.7, 2.5 Hz), 106.9 (J_{C-F} = 21.6, 4.5 Hz), 67.0, 65.1, 59.3, 55.2, 54.4, 51.1, 37.1, 25.7, 24.4, 21.2; ^{19}F NMR (470 MHz, MeOH-d_4) −112.0, −115.8 (br d, J = 6.0 Hz), −130.6 (dq, J = 17.9, 9.2 Hz), −132.7 (dt, J = 23.2, 10.2 Hz), −142.2 (dq, J = 22.0, 10.5, 9.7 Hz), −142.4 (dt, J = 20.7, 11.9 Hz); LRMS (ES$^+$) 111.3 (8), 263.3 (2), 292.4 (100), 331.4 (12), 439.4 (3); HRMS (ESI, [M − 1]$^+$) calcd for $C_{33}H_{29}N_2OF_6^+$ 583.2184, found 583.2172.



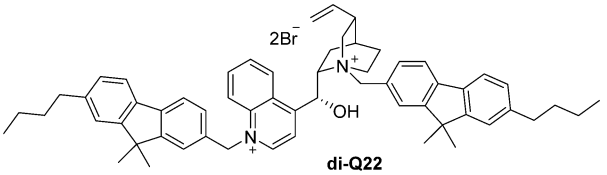
di-Q23

Data for ***di-Q23:*** ^{1}H NMR (500 MHz, MeOH-d_4) 9.65 (dt, J = 6.7, 1.5 Hz, 1 H), 8.79 (d, J = 8.4 Hz, 1 H), 8.70−8.64 (m, 1 H), 8.62 (d, J = 6.2 Hz, 1 H), 8.31−8.22 (m, 1 H), 8.19 (t, J = 7.8 Hz, 1 H), 8.09−8.03 (m, 1 H), 7.85 (br t, J = 7.0 Hz, 1 H), 7.77−7.63 (m, 6 H), 7.59 (d, J = 7.5 Hz, 2 H), 7.53 (t, J = 7.7 Hz, 1 H), 7.49 (dd, J = 9.0, 6.3 Hz, 2 H), 7.43 (td, J = 8.3, 7.8, 1.8 Hz, 2 H), 7.41−7.32 (m, 3 H), 6.95 (br s, 1 H), 6.51−6.43 (m, 2 H), 5.72 (ddd, J = 17.3, 10.5, 6.9 Hz, 1 H), 5.29 (br s, 2 H), 5.17 (d, J = 17.2 Hz, 1 H), 4.98 (br d, J = 10.5 Hz, 1 H), 4.49 (td, J = 11.5, 10.9, 4.6 Hz, 1 H), 4.17 (dd, J = 11.5, 6.9 Hz, 1 H), 3.89−3.76 (m, 1 H), 3.62−3.46 (m, 2 H), 2.79−2.71 (m, 1 H), 2.28 (br q, J = 11.1 Hz, 1 H), 2.13−2.05 (m, 1 H), 1.97−1.87 (m, 1 H), 1.57 (tdd, J = 12.5, 7.9, 4.5 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 158.1, 149.7, 140.9, 140.7, 139.3, 139.3, 138.1, 137.2, 135.4, 134.4, 132.8, 132.1, 130.7, 129.8, 129.5, 129.0, 129.0, 128.6, 128.3, 127.9, 127.9, 127.2, 126.9, 126.8, 126.5, 126.2, 126.1, 121.6, 120.0, 116.6, 67.2, 64.8, 62.4, 60.0, 59.6, 50.8, 36.9, 26.0, 24.3, 21.2; LRMS (ES$^+$) 314.5 (100), 417.4 (2), 461.4 (7), 462.5 (4).



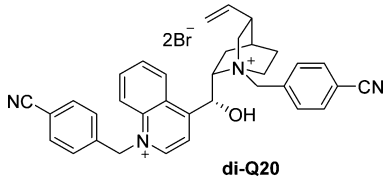
di-Q5

Data for ***di-Q5:*** ^{1}H NMR (500 MHz, MeOH-d_4) 9.63 (dd, J = 6.4, 1.6 Hz, 1 H), 8.83 (dd, J = 8.5, 1.5 Hz, 1 H), 8.63 (d, J = 8.9 Hz, 1 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.30 (ddd, J = 8.8, 7.1, 1.2 Hz, 1 H), 8.21 (ddd, J = 8.3, 7.0, 1.0 Hz, 1 H), 7.94 (td, J = 7.6, 1.7 Hz, 1 H), 7.67 (dtd, J = 9.9, 5.4, 1.7 Hz, 1 H), 7.53−7.48 (m, 2 H), 7.43 (td, J = 7.6, 1.2 Hz, 1 H), 7.38 (td, J = 9.0, 1.0 Hz, 1 H), 7.30−7.23 (m, 2 H), 6.95 (br s, 1 H), 6.48 (d, J = 15.6 Hz, 1 H), 6.44 (d, J = 15.6 Hz, 1 H), 5.76 (ddd, J = 17.3, 10.5, 7.0 Hz, 1 H), 5.36 (d, J = 12.5 Hz, 1 H), 5.20 (dt, J = 17.3, 1.0 Hz, 1 H), 5.20 (d, J = 11.5 Hz, 1 H), 5.01 (dt, J = 10.5, 1.2 Hz, 1 H), 4.54−4.44 (m, 1 H), 4.23 (br t, J = 9.3 Hz, 1 H), 3.86 (ddd, J = 12.6, 4.6, 3.3 Hz, 1 H), 3.59 (dd, J = 12.8, 10.6 Hz, 1 H), 3.38−3.32 (m, 1 H), 2.80−2.74 (m, 1 H), 2.31−2.22 (m, 2 H), 2.11 (br q, J = 3.8 Hz, 1 H), 1.97−1.88 (m, 1 H), 1.59 (td, J = 10.4, 3.4 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 161.8 (J_{C-F} = 249.0 Hz), 160.2 (J_{C-F} = 247.0 Hz), 158.6, 149.8, 138.1, 137.2, 136.0, 135.6, 133.2 (J_{C-F} = 9.0 Hz), 131.5 (J_{C-F} = 8.5 Hz), 130.6, 130.2, 127.0, 126.1, 125.2 (J_{C-F} = 17.5), 125.2 (J_{C-F} = 16.6 Hz), 121.5, 120.6 (J_{C-F} = 13.7 Hz), 119.6, 116.7, 116.4, 116.2 (J_{C-F} = 21.9 Hz), 115.2 (J_{C-F} = 13.7 Hz), 67.0, 65.0, 59.5, 56.4, 55.3, 51.0, 37.1, 25.8, 24.4, 21.1; ^{19}F NMR (470 MHz, MeOH-d_4) −111.9 (q, J = 9.7 Hz), −115.9 (q, J = 9.7 Hz); LRMS (ES$^+$) 111.3 (35), 133.1 (4), 157.1 (7), 179.1 (15), 256.3 (100), 295.4 (30), 403.3 (4); HRMS (ESI, [M − 1]$^+$) calcd for $C_{33}H_{33}N_2OF_2^+$ 511.2561, found 511.2555.



di-Q22

Data for ***di-Q22:*** ^{1}H NMR (500 MHz, MeOH-d_4) 9.60 (d, J = 6.2 Hz, 1 H), 8.76 (br t, J = 6.5 Hz, 2 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.30 (ddd, J = 8.8, 5.4, 1.2 Hz, 1 H), 8.20 (dd, J = 8.7, 7.0 Hz, 1 H), 7.89 (br s, 2 H), 7.77 (d, J = 7.8 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.70 (dd, J = 7.8, 1.8 Hz, 1 H), 7.66 (d, J = 7.8 Hz, 1 H), 7.63 (d, J = 1.7 Hz, 1 H), 7.37 (dd, J = 8.1, 1.8 Hz, 1 H), 7.35 (br d, J = 1.5 Hz, 1 H), 7.30 (br d, J = 1.5 Hz, 1 H), 7.21 (dd, J = 7.8, 1.6 Hz, 1 H), 7.17 (dd, J = 7.8, 1.6 Hz, 1 H), 6.96 (br s, 1 H), 6.44 (d, J = 15.3 Hz, 1 H), 6.40 (d, J = 15.3 Hz, 1 H), 5.74 (dddd, J = 17.4, 10.7, 7.0 3.7 Hz, 1 H), 5.27 (d, J = 12.4 Hz, 1 H), 5.21 (d, J = 12.2 Hz, 1 H), 5.19 (d, J = 17.1 Hz, 1 h), 5.00 (td, J = 10.7, 1.1 Hz, 1 H), 4.49 (dt, J = 14.2, 6.8 Hz, 1 H), 4.16 (br t, J = 14.2, 6.8 Hz, 1 H), 3.81 (dt, J = 12.7, 10.8, 4.8 Hz, 1 H), 3.57 (dd, J = 12.8, 10.7 Hz, 1 H), 3.49 (td, J = 11.3, 10.8, 4.8 Hz, 1 H), 2.80−2.73 (m, 1 H), 2.70 (dt, J = 15.6, 7.7 Hz, 4 H), 2.34−2.23 (m, 2 H), 2.11 (dq, J = 6.1, 3.2 Hz, 1 H), 1.98−1.88 (m, 1 H), 1.71−1.60 (m, 5 H), 1.55 (s, 3 H), 1.51 (s, 3 H), 1.44 (s, 6 H), 1.40 (ddd, J = 14.9, 10.2, 4.7 Hz, 4 H), 0.97 (dt, J = 9.0, 7.4 Hz, 6 H); ^{13}C NMR (126 MHz, DMSO-d_6) 158.0, 154.0, 153.9, 153.7, 149.4, 142.8, 142.2, 140.5, 139.4, 138.2, 137.2, 135.3, 132.8, 132.1, 130.6, 128.2, 128.2, 127.4, 127.2, 126.7, 126.1, 125.9, 122.7, 122.6, 122.5, 121.6, 120.5, 120.3, 120.2, 120.1, 120.0, 116.6, 67.1, 64.8, 62.0, 60.4, 59.4, 50.6, 46.4, 46.4, 36.8, 35.2, 35.2, 33.4, 26.9, 26.8, 26.1, 24.2, 21.9, 21.9, 21.2, 13.8, 13.8; LRMS (ES$^+$) 111.3 (80), 129.3 (12), 263.3 (20), 382.6 (12), 410.7 (80), 501.8 (12), 557.6 (85), 558.6 (40); HRMS (ESI, [M − 1]$^+$) calcd for $C_{59}H_{67}N_2O^+$ 819.5253, found 819.5226.



di-Q20

Data for ***di-Q20:*** ^{1}H NMR (400 MHz, MeOH-d_4) 9.67 (d, J = 6.2 Hz, 1 H), 8.84 (dd, J = 8.2, 1.7 Hz, 1 H), 8.64 (d, J = 6.1 Hz, 1 H), 8.47 (dd, J = 8.9, 1.2 Hz, 1 H), 8.25 (ddd, J = 8.8, 7.0, 1.5 Hz, 1 H), 8.20 (ddd, J = 8.1, 7.0, 1.3 Hz, 1 H), 8.03 (d, J = 8.3 Hz, 2 H), 7.95 (d, J = 8.3 Hz, 2 H), 7.80 (d, J = 8.3 Hz, 2 H), 7.56 (d, J = 8.3 Hz, 2 H), 6.93 (br s, 1 H), 6.52 (br d, J = 2.6 Hz, 2 H), 5.77 (ddd, J = 17.3, 10.5, 7.0 Hz, 1 H), 5.37 (d, J = 12.2 Hz, 1 H), 5.30 (J = 12.2 Hz, 1 H), 5.22 (dt, J = 17.1, 1.2 Hz, 1 H), 5.01 (J = 10.6, 1.2 Hz, 1 H), 4.54−4.42 (m, 1 H), 4.23 (br t, J = 9.3 Hz, 1 H), 3.90 (dt, J = 12.6, 4.0 Hz, 1 H), 3.48 (dd, J = 12.6, 10.7 Hz, 1 H), 3.41 (dd, J = 11.8, 5.0 Hz, 1 H), 2.79−2.71 (m, 1 H), 2.35−2.21 (m, 2 H), 2.16−2.08 (m, 1 H), 1.97−1.86 (m, 1 H), 1.66 (td, J = 13.3, 12.7, 3.1 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 159.2, 150.6, 138.2, 137.8, 137.0, 136.0, 134.5, 134.3,

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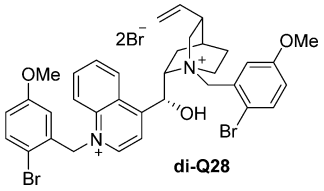
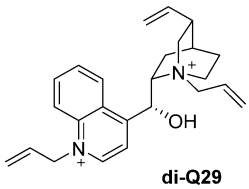
134.2, 134.1 133.9, 131.0, 130.9, 129.6, 129.5, 127.7, 126.1, 121.7, 119.7, 117.8, 116.8, 116.7, 115.7, 110.2, 67.3, 65.5, 60.4, 59.6, 58.7, 51.4, 37.2, 25.7, 24.4, 21.3; LRMS (ES^+) 111.3 (25), 133.1 (3), 179.1 (3), 263.4 (100), 264.0 (55), 302.5 (35), 410.4 (9); HRMS (ESI, $[M - 1]^+$) calcd for $C_{35}H_{33}N_4O^+$ 525.2654, found 525.2649.



di-Q28

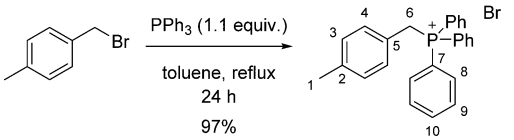
Data for ***di-Q28****:* ^{1}H NMR (500 MHz, MeOH-d_4) 9.31 (d, J = 6.2 Hz, 1 H), 8.87 (dd, J = 1.4, 8.7 Hz, 11 H), 8.57 (d, J = 6.5 Hz, 1 H), 8.56 (d, J = 9.7 Hz, 1 H), 8.35 (ddd, J = 1.3, 7.0, 8.7 Hz, 1 H), 8.26 (ddd, J = 1.0, 6.9, 8.1 Hz, 1 H), 7.74 (d, J = 8.9 Hz, 1 H), 7.72 (d, J = 8.9 Hz, 1 H), 7.64 (d, J = 3.1 Hz, 1 H), 7.12 (dd, J = 3.0, 8.9 Hz, 1 H), 7.05 (dd, J = 3.0, 8.9 Hz, 1 H), 6.96 (br s, 1 H), 6.77 (d, J = 3.0 Hz, 1 H), 6.37 (q, J = 15.7 Hz, 2 H), 5.75 (ddd, J = 6.7, 10.6, 17.2 Hz, 1 H), 5.48 (d, J = 12.5 Hz, 1 H), 5.32 (d, J = 12.6 Hz, 1 H), 5.23 (dt, J = 1.1, 17.5 Hz, 1 H), 5.01 (dt, J = 1.1, 10.7 Hz, 1 H), 4.72 (tt, J = 3.5, 11.1 Hz, 1 H), 4.23 (t, J = 9.2 Hz, 1 H), 4.04 (dt, J = 3.7, 12.6 Hz, 1 H), 3.92 (s, 3 H), 3.75 (s, 3 H), 3.68 (dd, J = 10.6, 12.6 Hz, 1 H), 3.38 (td, J = 4.7, 11.7 Hz, 1 H), 2.82–2.74 (m, 1 H), 2.29–2.18 (m, 2 H), 2.13–2.09 (m, 1 H), 1.95–1.85 (m, 1 H), 1.51 (ddt, J = 3.5, 10.0, 13.4 Hz, 1 H); HRMS (ESI, $[M - 1]^+$) calcd for $C_{35}H_{37}N_2O_3Br_2^+$ 691.1171, found 691.1160.



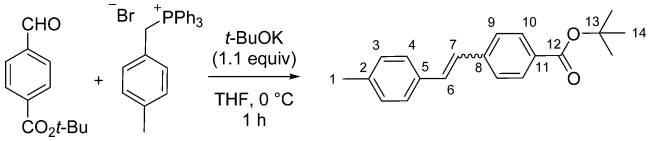
di-Q29

Data for ***di-Q29****:* ^{1}H NMR (500 MHz, MeOH-d_4) 9.52 (dd, J = 1.8, 6.2 Hz, 1 H), 8.64 (dd, J = 2.0, 8.6 Hz, 1 H), 8.61 (d, J = 9.2 Hz, 1 H), 8.51 (d, J = 6.2 Hz, 1 H), 8.32 (ddd, J = 1.3, 7.0, 8.8 Hz, 1 H), 8.19 (ddd, J = 1.2, 7.0, 8.3 Hz, 1 H), 6.68 (br s, 1 H), 6.39–6.24 (m, 2 H), 5.98 (dd, J = 1.5, 17.0 Hz, 1 H), 5.88 (dd, J = 1.2, 10.2 Hz, 1 H), 5.80–5.76 (m, 2 H), 5.75–5.69 (m, 1 H), 5.53 (d, J = 10.5 Hz, 1 H), 5.44 (dd, J = 1.5, 17.2 Hz, 1 H), 5.19 (dd, J = 1.2, 17.2 Hz, 1 H), 5.00 (dt, J = 1.2, 10.5 Hz, 1 H), 4.67 (dd, J = 7.6, 12.9 Hz, 1 H), 4.50 (ddd, J = 1.3, 6.7, 12.7 Hz, 1 H), 4.33 (dddd, J = 3.2, 5.4, 10.9, 12.5 Hz, 1 H), 3.96 (t, J = 9.1 Hz, 1 H), 3.84 (dd. J = 10.5, 13.1 Hz, 1 H), 3.67–3.56 (m, 2 H), 2.94–2.86 (m, 1 H), 2.28 (dddd, J = 3.6, 5.2, 10.9, 12.8 Hz, 1 H), 2.19 (ddt, J = 2.0, 7.9, 13.4 Hz, 1 H), 2.13 (dq, J = 3.2, 6.5 Hz, 1 H), 2.05 (tdt (2.9, 5.4, 11.4 Hz, 1 H), 1.53 (tq, J = 3.5, 10.0 Hz, 1 H); ^{13}C NMR (126 MHz, DMSO-d_6) 158.0, 149.2, 138.3, 137.3, 135.4, 131.5, 130.5, 127.7, 126.5, 126.5, 126.1, 121.6, 120.9, 120.2, 116.8, 66.1, 64.9, 62.0, 60.4, 59.4, 51.9, 37.4, 26.1, 24.7, 21.0; HRMS (ESI, $[M - 1]^+$) calcd for $C_{25}H_{31}N_2O^+$ 375.2436, found 375.2427.

6.7. Synthetic Intermediates Used in Catalyst Syntheses.



Preparation of (4-Methylbenzyl)triphenylphosphonium Bromide. To a flame-dried, 500-mL, single-neck, round-bottomed flask fitted with stir bar and reflux condenser was added 4-methylbenzyl bromide (5.00 g, 27.02 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar, and then toluene was added (100 mL). The reaction was stirred at rt to give a homogeneous, colorless solution. Triphenylphosphine (7.80 g, 29.72 mmol, 1.0 equiv) was added in one portion, and then the reaction was heated to reflux in an oil bath (oil bath temp = 120 °C) for 24 h, over which time a white precipitate formed. After 24 h, the flask was removed from the oil bath and cooled to rt. The white precipitate was collected by filtration (Büchner funnel) and washed with an excess of cyclohexane. The solid was collected and dried under high vacuum (0.1 mmHg) at rt for 12 h to yield (4-methylbenzyl)phosphonium bromide as a white powder (11.68 g, 97%). This material was sufficiently pure to used as is in the next reaction. An analytically pure sample can be obtained by recrystallization according to the following procedure. A small portion of material (300 mg) was taken up in a minimum (30 mL) of boiling hexanes, and to this hot solution was added MeOH dropwise until a homogeneous solution was obtained (1 mL). The colorless solution was then allowed to stand undisturbed at room temperature until crystallization was observed and then cooled to −20 °C overnight. The colorless square crystals were collected by Büchner filtration, washed with cold (−20 °C) 30:1 hexanes/MeOH, and then dried under high vacuum at rt (0.1 mmHg). Data for 4-methylbenzylphosphonium bromide: mp 268–270 °C (hexanes/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) 7.79–7.67 (m, 9 H), 7.65–7.59 (m, 6 H), 6.92 (dd, J = 2.4, 8.3 Hz, 2 H), 6.88 (d, J = 8.3 Hz, 2 H), 5.31 (d, J = 14.3 Hz, 2 H, $H_2C(6)$), 3.16 (s, 3 H, $H_3C(1)$); ^{13}C NMR (126 MHz, $CDCl_3$) 138.4 (J_{C-P} = 4.1 Hz), 135.0 (J_{C-P} = 3.2 Hz), 134.4 (J_{C-P} = 9.7 Hz), 131.4 (J_{C-P} = 6.0 Hz), 130.2 (J_{C-P} = 12.4 Hz), 129.6 (J_{C-P} = 3.2 Hz), 123.7 (J_{C-P} = 8.8 Hz), 117.9 (J_{C-P} = 85.6 Hz), 30.6 ($H_2C(6)$, J_{C-P} = 47.0 Hz), 21.2 ($H_3C(1)$); IR (ATR-FTIR) 3032 (w), 3010 (w), 2858 (w), 1516 (w), 1436 (w), 1106 (w), 994 (w), 820 (w), 740 (w), 718 (w), 713 (w), 686 (w), 553 (w), 499 (w); LRMS (ES^+) 367.6 (100), 368.5 (30), 369.5 (5). Anal. Calcd for $C_{26}H_{24}BrP$ (447.36): C, 69.81 H, 5.41. Found: C, 69.57 H, 5.41.



Preparation of tert-Butyl 4-(4-Methylstryryl)benzoate. To a flame-dried, 500-mL, three-neck, round-bottomed flask fitted with an Ar inlet, internal temperature probe, and large magnetic stir bar was added (4-methylbenzyl)phosphonium bromide (3.24 g, 7.23 mmol, 1.05 equiv). The flask was evacuated and backfilled with Ar twice. To a separate 100-mL conical flask with an Ar inlet were added *tert*-butyl 4-formylbenzoate[67] (1.42 g, 6.89 mmol, 1.0 equiv) and THF (40 mL), and this solution was added to the reaction flask by cannula. Following addition, additional THF was added (58 mL) to give a white suspension. The reaction mixture was cooled in an ice–water bath (internal temp = 1.1 °C), and the potassium *tert*-butoxide (0.85 g, 7.58 mmol, 1.1 equiv) was added as a solid in a single portion. The reaction turned a bright yellow-orange immediately after the addition of base. The reaction was stirred at 0 °C for 1 h and 15 min, and then the ice–water bath was removed and the reaction was stirred at rt overnight (18 h). The reaction was then quenched by the addition of 50 mL of distilled H_2O. The reaction mixture was split into two portions and transferred to a 250-mL separatory funnel with dichloromethane (30 mL). The organic phase was separated, the aqueous layer was extracted with dichloromethane (2 × 30 mL), and the combined organic layer was washed with saturated brine solution (1 × 50 mL). The organic extractions were concentrated by rotary evaporation to an approximate volume of 15 mL. The crude reaction solution was the triturated with hexanes (200 mL) to precipitate triphenylphosphine oxide. The white precipitate was separated by filtration and rinsed with a large amount of hexanes. The filtrate was concentrated and dried under reduced pressure (0.1 mmHg) to yield the crude material as a fluffy white solid. Purification by flash chromatography (SiO_2, dry load on Celite, 20 mL fractions, hexanes/THBE gradient elution: 100% hexanes (200 mL) to 9:1 hexanes/TBME (600 mL)) yielded *tert*-butyl-4-(4-methylstyryl)benzoate as a shiny white solid (0.88 g, 76%) as a 2:1 mixture of E/Z isomers. An analytical sample was purified by recrystallization from boiling hexanes. A small portion of the material (330 mg) was taken up in a minimum of boiling hexanes (10 mL), subjected to a hot filtration (Kimwipe), reheated to homogeneity, and then allowed to cool slowly to rt over 3 h, at which time crystal formation was evident. The flask was further cooled to −20 °C for 18 h. The white needles were collected by Büchner filtration, rinsed with

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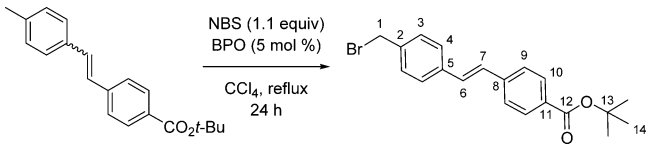
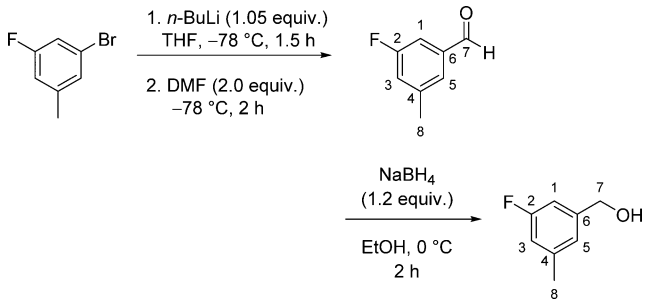
an excess of cold (−20 °C) hexanes, crushed with a spatula, and dried under reduced pressure (0.1 mmHg) at rt for 24 h to yield *tert*-butyl 4-(4-methyl)styryl)benzoate as white crystals (133 mg, 40% recovery). The material was obtained as a mixture of both *E* and *Z* geometric isomers (2:1); however, ^{1}H and ^{13}C NMR signals are reported separately for simplification. Data for *tert*-butyl 4-(4-methylstyryl)-benzoate: mp 138 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 7.96 (d, J = 8.4 Hz, 2 H, HC(10)-*E*), 7.84 (d, J = 8.3 Hz, 2 H, HC(10)-*Z*), 7.53 (d, J = 8.4 Hz, 2 H, HC(9)-*E*), 7.43 (d, J = 8.2 Hz, 2 H, HC(3)-*E*), 7.29 (d, J = 8.5 Hz, 2 H, HC(9)-*Z*), 7.18 (d, J = 8.4 Hz, 2 H, HC(4)-*E*), 7.11 (d, J = 8.3 Hz, 2 H, HC(3)-*Z*), 7.08 (d, J = 16.3 Hz, 1 H, HC(7)-*E*), 7.04 (d, J = 16.3 Hz, 1 H, HC(6)-*E*), 7.03 (d, J = 8.3 Hz, 2 H, HC(4)-*Z*), 6.65 (d, J = 12.4 Hz, 1 H, HC(7)-*Z*), 6.55 (d, J = 12.0 Hz, 1 H, HC(6)-*Z*), 2.37 (s, 3 H, H_3C(1)-*E*), 2.32 (s, 3 H, H_3C(1)-*Z*), 1.60 (s, 9 H, H_3C(14)-*E*), 1.58 (s, 9 H, H_3C(14)); ^{13}C NMR (126 MHz, $CDCl_3$) 165.8, 142.0, 141.7, 138.3, 137.4, 134.2, 133.9, 132.0, 130.9, 130.7, 130.5, 130.0, 129.6, 129.5, 129.2, 128.9, 128.8, 126.8, 126.2, 81.0, 28.4, 21.5. IR (ATR-FTIR) 2983 (w), 2930 (w), 1707 (m), 1596 (m), 1369 (w), 1284 (m), 1257 (w), 1159 (m), 1110 (m), 967 (w), 947 (w), 807 (m), 767 (w), 713 (w), 530 (m); LRMS (TOF ES$^+$) 221.1 (7), 239.1 (100), 240.1 (22), 295.2 (10); HRMS (ESI, $[M + 1]^+$) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1703; TLC R_f 0.36 (silica gel, 20:1 hexanes/TBME) [UV]. Anal. Calcd for $C_{20}H_{22}O_2$ (294.16): C, 81.60; H, 7.53. Found: C, 81.65; H, 7.34.



Preparation of tert-Butyl 4-(4-Bromomethylstyryl)benzoate. To a flame-dried, 10-mL Schlenk flask fitted with a stir bar and septum was added *tert*-butyl 4-(4-methylstyryl)benzoate (400 mg, 1.36 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar, and carbon tetrachloride (3.7 mL) was added to give a homogeneous, colorless solution. The reaction flask was fitted with a reflux condenser and heated to reflux (oil bath = 77 °C). To the hot solution were added *N*-bromosuccinimide (266 mg, 1.49 mmol, 1.1 equiv) and benzoyl peroxide (16.5 mg, 0.07 mmol, 5 mol %). The reaction was heated at reflux for 24 h and then was cooled to rt. The reaction was filtered through a Kimwipe to remove residual succinimide, rinsed with an excess of CCl_4, and concentrated by rotary evaporation to give crude *tert*-butyl 4-(4-methylstyryl)benzoate as a pale yellow solid (759 mg, 100%). Purification was performed by recrystallization as the compound was not stable to silica gel chromatography. The crude material was taken up in a minimum of boiling hexanes (50 mL), subjected to a hot filtration to remove insoluble material, and rinsed with excess boiling hexanes, and the homogeneous, pale yellow filtrate was reduced to a volume of approximately 35 mL. The flask was allowed to cool slowly to rt for 3 h, at which time crystal formation was evident. The flask was further cooled to −20 °C for 18 h. The flocculent shiny white flakes were collected by Büchner filtration, rinsed with an excess of cold (−20 °C) hexanes, crushed with a spatula, and dried under reduced pressure (0.1 mmHg) at rt for 24 h to yield *tert*-butyl 4-(4-bromomethyl)styryl)benzoate as white crystals (203 mg, 40%). Data for *tert*-butyl 4-(4-bromomethylstyryl)benzoate: mp 150−151 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 7.98 (d, J = 8.5 Hz, 2 H, HC(10)), 7.54 (d, J = 8.5 Hz, 2 H, HC(9)), 7.51 (d, J = 8.3 Hz, 2 H, HC(4)), 7.40 (d, J = 8.3 Hz, 2 H, HC(3)), 7.18 (d, J = 16.3 Hz, 1 H, HC(7)), 7.13 (d, J = 16.3 Hz, 1 H, HC(6)), 4.52 (s, 2 H, H_2C(1)), 1.61 (s, 9 H, H_3C(14)); ^{13}C NMR (126 MHz, $CDCl_3$) 165.7 (O═C(12)), 141.2 (C(11)), 137.7 (C(2)), 137.2 (C(5)), 131.2 (C(8)), 130.2 (HC(7)), 130.0 (HC(10)), 129.7 (HC(3)), 128.6 (HC(6)), 127.2 (HC(4)), 126.4 (HC(9)), 81.2 (C(13)), 33.5 (H_2C(1)), 28.4 (H_3C(14)); IR (ATR-FTIR) 2983 (w), 2970 (w), 2930 (w), 1703 (m), 1596 (w), 1471 (w), 1387 (w), 1279 (m), 1248 (m), 1159 (m), 1097 (m), 867 (m), 838 (m), 767 (m), 700 (m), 611 (m), 557 (w), 521 (w); LRMS (TOF ES$^+$) 239.1 (60), 269.1 (12), 293.2 (36), 294.2 (11), 317.0 (100), 318.0 (15), 319.0 (100), 320 (15), 373.1 (14), 375.1 (13); TLC R_f 0.26 (silica gel, 20:1 hexanes/TBME) [UV,I_2]. Anal. Calcd for $C_{20}H_{21}BrO_2$ (373.29): C, 64.35; H, 5.67. Found: C, 64.51; H, 5.73.



Preparation of 3-Fluoro-5-methylbenzyl Alcohol. To a flame-dried, 250-mL round-bottomed flask equipped with a stir bar, septum, Ar inlet, and internal temperature probe was added 3-bromo-5-fluorotoluene (2.00 g, 10.58 mmol, 1.0 equiv) by syringe. THF (53 mL) was added, and the colorless solution was stirred at rt. The reaction mixture was then cooled in a dry ice/acetone bath (internal temp = −74 °C), and 2.43 M *n*-butyl lithium in hexanes (4.75 mL, 11.52 mmol, 1.09 equiv) was added dropwise by syringe at a rate in which the internal temperature was maintained below −72 °C to give a pale yellow homogeneous solution. This solution was stirred at −78 °C for 1.5 h, and then DMF (1.64 mL, 21.6 mmol, 2.0 equiv) was added by syringe over 15 min while the internal temperature was maintained below −68 °C, and then the solution was stirred at −78 °C for an additional 2 h, over which time the reaction mixture became cloudy. The reaction was then quenched by pouring directly into 100 mL of 5% aqueous $NaHCO_3$ solution at rt. The reaction mixture was transferred to a 250-mL separatory funnel with Et_2O (75 mL), and the two phases were separated. The aqueous phase was extracted with Et_2O (2 × 60 mL), and the combined organics were washed with water (5 × 100 mL) in order to remove residual DMF, washed with brine (1 × 100 mL), dried over Na_2SO_4, and concentrated by rotary evaporation without heating to yield 2.04 g of a pale yellow oil (>100%). Solvent was not completely removed from crude material due to high volatility of the benzaldehyde and the crude material was stored under Ar to prevent oxidation prior to use in the next step. Data for crude benzaldehyde: ^{1}H NMR (500 MHz, $CDCl_3$) 9.95 (d, J = 1.8 Hz, 1H. OHC(7)), 7.48 (br s, 1H, HC(3)), 7.36 (br dt, J = 8.4, 1.8 Hz, 1H, HC(1)), 7.15 (br ddt, J = 1.0, 2.2, 9.3 Hz, 1H, HC(5)), 2.44 (s, 3H, H_3C(8)); ^{13}C NMR (126 MHz, $CDCl_3$) 191.2 (d, J_{C-F} = 2.0 Hz, OHC(7)), 163.1 (d, J_{C-F} = 248.7 Hz, FC(2)), 141.7 (d, J_{C-F} = 7.4 Hz, OHCC(6)), 138.3 (d, J_{C-F} = 6.6 Hz, H_3CC(4)), 126.8 (d, J_{C-F} = 2.5 Hz, HC(5)), 122.2 (d, J_{C-F} = 21.6 Hz, HC(1)), 112.7 (d, J_{C-F} = 22.0 Hz, HC(3)), 21.2 (d, J_{C-F} = 1.6 Hz, H_3C(8)); ^{19}F NMR (470 MHz, $CDCl_3$) −113.0 (t, J = 8.6 Hz); IR (ATR-FTIR) 2823 (w), 1700 (s), 1620 (w), 1591 (m), 1463 (w), 1387 (m), 1296 (s), 1153 (m), 1144 (m), 1122 (m), 1024 (w), 976 (m), 950 (m), 857 (m), 707 (s), 672 (s), 546 (w), 507 (w), 482 (w); LRMS (TOF-MS, EI$^+$) 57.0 (3), 83.0 (9), 107.0 (10), 109.0 (55), 111.1 (7), 137.0 (100), 138.0 (50), 139.1 (18); TLC R_f 0.41 (silica gel, 9:1 hexanes/TBME) [UV]. To the 100-mL round-bottomed flask containing crude 3-fluoro-5-methylbenzaldehyde (2.04 g, ∼10.58 mmol, 1.0 equiv) was added a stir bar, Ar inlet, and dry EtOH (42 mL). The reaction was stirred under Ar and cooled in an ice−water bath for 15 min. Then sodium borohydride (0.48 g, 12.59 mmol, 1.2 equiv) was added in one portion and the reaction was stirred at 0 °C for 2 h, after which time the reaction was complete as determined by TLC analysis (9:1 hexanes/TMBE). The reaction was quenched by slow addition of saturated aqueous NH_4Cl (20 mL) at 0 °C until gas evolution halted. The reaction mixture was then concentrated by rotary evaporation without heat to remove a majority of the EtOH, and then was transferred to a 125-mL separatory funnel with dichloromethane (40 mL) and distilled water (20 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine (1 × 40 mL), dried over $MgSO_4$, filtered (Kimwipe), and concentrated by rotary evaporation (no heat) to give a colorless oil (2.94 g, > 100%). The crude oil was purified by

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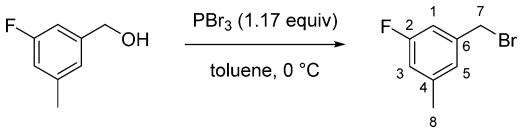
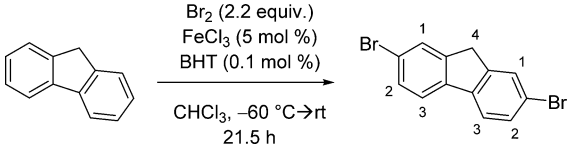
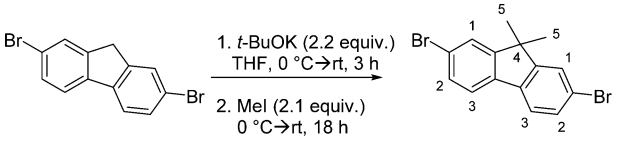
Kugelrohr distillation (air bath = 160 °C, 20 mbar) to give a colorless oil (1.33 g, 90% over two steps). An analytical sample was obtained by a second distillation under the same conditions. Data for 3-fluoro-5-methylbenzaldehyde: bp 160 °C (air bath, 15 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) 6.89 (br s, 1 H, HC(3)), 6.88 (br d, J = 9.4 Hz, 1 H, HC(1)), 6.80 (br d, J = 9.6 Hz, 1 H, HC(5)), 4.65 (s, 2 H, $H_2C(7)$), 2.35 (s, 3 H, $H_3C(8)$); ^{13}C NMR (126 MHz, $CDCl_3$) 163.1 (, J_{C-F} = 245.2 Hz, F−C(2)), 143.2 (J_{C-F} = 7.9 Hz, $HOCH_2C(6)$), 140.7 (J_{C-F} = 8.0 Hz, $H_3CC(4)$), 123.1 (J_{C-F} = 2.7 Hz, HC(5)), 115.1 (J_{C-F} = 21.2 Hz, HC(1)), 110.8 (J_{C-F} = 21.4 Hz, HC(3)), 64.7 (J_{C-F} = 2.3 Hz, $H_2C(7)$), 21.4 (J_{C-F} = 1.9 Hz, $H_3C(8)$); IR (ATR-FTIR) 3308 (w), 2923 (w), 1623 (w), 1590 (w), 1461 (m), 1300 (m), 1150 (w), 1129 (m), 1036 (m), 1010 (m), 935 (m), 844 (s), 681 (m), 648 (m), 565 (w), 542 (m) 512 (w), 487 (w); LRMS (EI$^+$, 70 eV) 77.0 (20), 83.0 (22), 91.0 (28), 97.0 (65), 109.0 (70), 125.0 (71), 140.0 (100); TLC R_f 0.07 (silica gel, 9:1 hexanes/TBME) [UV]. Anal. Calcd for C_8H_9FO (140.16): C, 68.56; H, 6.47. Found: C, 68.31; H, 6.53.



Preparation of 3-Fluoro-5-methylbenzyl Bromide. To a flame-dried, two-necked, 250-mL round-bottomed flask fitted with an Ar inlet, internal temperature probe, and magnetic stir bar was added 3-fluoro-5-methylbenzyl alcohol (1.00 g, 7.13 mmol, 1.0 equiv) as a solution in toluene (40 mL) by cannula. The colorless, homogeneous solution was cooled in a ice−salt water bath (I.T. = −1 °C), and then phosphorus tribromide (0.78 mL, 8.35 mol, 1.17 equiv) was added dropwise by syringe over a 5 min period while the internal temperature was maintained below 5 °C. After addition, the reaction was stirred at 0 °C for 3 h and was then quenched by the addition of saturated aqueous Na_2CO_3 (50 mL). The reaction mixture was transferred to a 250-mL separatory funnel with dichloromethane (50 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layer was washed with distilled H_2O (1 × 40 mL) and saturated brine solution (1 × 40 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to give the crude material as a colorless oil (0.7 g, 50% mass recovery). Purification by Kugelrohr distillation (air bath = 135 °C at 25 mbar) yielded 3-fluoro-5-methylbenzyl bromide as a low-melting white crystalline solid (527 mg, 38%).). An analytical sample was obtained by a second distillation under the same conditions. Data for 3-fluoro-5-methylbenzyl bromide: bp 135 °C (air bath, 15 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) 6.98 (br s, 1 H, HC(5)), 6.91 (br d, J = 9.1 Hz, 1 H, HC(3)), 6.82 (br d, J = 9.4 Hz, 1 H, HC(1)), 4.42 (s, 2 H, $H_2C(7)$), 2.34 (s, 3 H, $H_3C(8)$); ^{13}C NMR (126 MHz, $CDCl_3$) 162.8 (J_{C-F} = 246.3 Hz, F−C(2)), 141.0 (J_{C-F} = 7.8 Hz, C(4)), 139.7 (J_{C-F} = 7.8 Hz, C(6)), 125.5 (J_{C-F} = 2.3 Hz, HC(5)), 116.2 (J_{C-F} = 21.2 Hz, HC(3)), 113.1 (J_{C-F} = 22.1 Hz, HC(1)), 32.7 (J_{C-F} = 2.3 Hz, $H_2C(7)$), 21.4 (J_{C-F} = 1.8 Hz, $H_3C(8)$). IR (ATR-FTIR) 2974 (w), 2920 (w), 1623 (m), 1591 (m), 1458 (w), 1306 (m), 1213 (m), 1132 (m), 1020 (w), 971 (m), 851 (m), 691 (s), 601 (s), 512 (w); LRMS (EI, 70 eV) 123.0 (100), 201.9 (12), 202.9 (3), 203.9 (12), 204.9 (3). TLC R_f 0.66 (silica gel, 20:1 hexanes/TBME) [UV]; Anal. Calcd for C_8H_8FBr (203.05): C, 47.32; H, 3.97. Found: C, 47.30; H, 3.96.



Preparation of 2,7-Dibromo-9H-fluorene.[68] To a flame-dried, 250-mL, three-neck round-bottomed flask fitted with an Ar inlet, septum, internal temperature probe, and 25-mL addition funnel were added fluorene (6.80 g, 40.91 mmol, 1.0 equiv) and BHT (0.01 g, 0.05 mmol, 0.1 mol %). The flask was evacuated and backfilled with Ar, $CHCl_3$ (50 mL) was added, and the mixture was stirred at rt to give a colorless, homogeneous solution. Under a stream of Ar were added ferric chloride (0.2 g, 1.23 mmol, 3 mol %) and an additional 50 mL of $CHCl_3$ to give a heterogeneous black-yellow solution. This solution was then cooled to −60 °C in a dry ice/acetone bath. The addition funnel was charged with bromine (4.61 mL, 90.00 mmol, 2.2 equiv). Under stirring, bromine was then added dropwise over 5 min while the internal temperature was maintained below −50 °C to give a red-brown solution. The bath was allowed to warm to room temperature overnight (21.5 h). The reaction was then quenched at rt by the addition of saturated aqueous Na_2SO_3 (100 mL) and stirred at rt for 1 h (loss of color completely over time). The reaction mixture was transferred to a 250-mL separatory funnel with dichloromethane (50 mL). The insoluble material was removed by filtration (Kimwipe) into another separatory funnel, this solution was extracted with dichloromethane (3 × 100 mL), and the combined organic layers were washed with brine (1 × 150 mL), dried over $MgSO_4$, filtered (Kimwipe), and concentrated by rotary evaporation to afford a poor recovery of a pale yellow solid (9.67 g, 73%). The previously insoluble filtrate at the beginning of the workup was redissolved in EtOAc (150 mL) and recombined with the retained aqueous layer from above. This mixture was extracted with EtOAc (3 × 100 mL), and the combined organic layers were dried over Na_2SO_4, filtered (Kimwipe), and concentrated by rotary evaporation to yield an addition 3.51 g of a pale yellow solid (26%). All of the combined crude solid (13.81 g) was dissolved in a minimum of boiling EtOH (200 mL) and submitted to a hot filtration (cotton plug). The solution began to crystallize at rt and was then cooled to −20 °C for 3 h. The crystals were collected by Büchner filtration and rinsed with an excess of cold (−20 °C) ethanol to yield pale orange needles (3.57 g, 27%). The mother liquor from this recrystallization and any insoluble material recovered from hot filtration was recombined, dried under high vacuum (0.1 mmHg) and recrystallized for a second crop from chloroform. The crude yellow material was dissolved in a minimum of boiling chloroform (90 mL), submitted to a hot filtration (Kimwipe), and then reduced to a volume of approximately 75 mL. The flask was allowed to cool to rt (no crystal formation) and then cooled in an ice−water bath to induce crystallization. This flask was then cooled to −20 °C overnight. The crystalline material was collected by Büchner filtration, rinsed with cold (−20 °C) chloroform, and dried under reduced pressure (0.1 mmHg) to give pale yellow shiny flakes (7.87 g, 59%). Data for 2,7-dibromo-9*H*-fluorene: mp 163−164 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.67 (br d, J = 1.7 Hz, 2 H, HC(1)), 7.60 (d, J = 8.1 Hz, 2 H, HC(3)), 7.50 (dd, J = 8.1, 1.7 Hz, 2 H, HC(2)), 3.87 (s, 2 H, $H_2C(4)$). IR (ATR-FTIR) 1453 (w), 1391 (w), 1158 (w), 1054 (w), 1005 (w), 952 (w), 932 (w), 858 (w), 833 (w), 807 (m), 685 (w), 661 (w), 498 (m); LRMS (TOF-AP$^+$) 149.02 (22), 163.05 (30), 165.07 (75), 166.07 (10), 242.98 (80), 243.98 (40), 244.98 (82), 245.98 (40), 321.90 (50), 323.90 (100), 325.90 (50); HRMS (ESI, $[M - 1]^-$) calcd for $C_{13}H_7Br_2$ 320.8915, found 320.8909; TLC R_f 0.67 (silica gel, 20:1 hexanes/TBME) [UV].



Preparation of 9,9-Dimethyl-2,7-dibromofluorene. To a flame-dried, 500-mL, two-necked, round-bottomed flask fitted with an Ar inlet, stir bar, septum, and internal temperature probe was added 2,7-dibromo-9*H*-fluorene (10.68 g, 32.96 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar. THF (70 mL) was added, and the reaction was stirred at rt to give a colorless solution. The solution was cooled in an ice−water bath (I.T. = 1 °C), and then potassium *tert*-butoxide (8.14 g, 72.50 mmol, 2.2 equiv) was added as a solid portionwise at a rate in which the internal temperature was maintained below 5 °C to give a deep purple solution. After full addition, the ice−water bath was removed, and the solution was stirred at rt for 3 h. The reaction mixture was then cooled in an ice−water bath, and methyl iodide (4.31 mL, 69.21 mmol, 2.1 equiv) was added by syringe (exotherm to 18 °C) to give an immediate chalky precipitate. The

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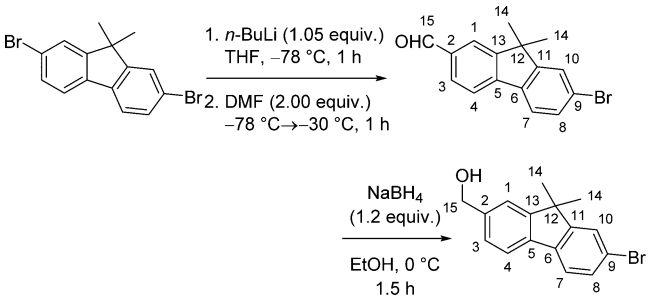
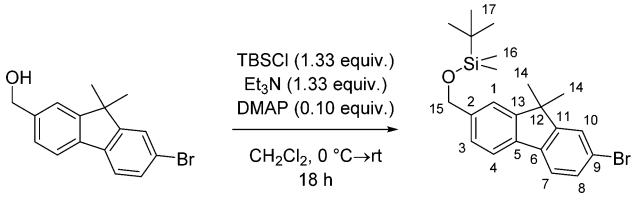
ice−water bath was then removed after the initial exotherm, and the reaction was stirred at rt overnight (18 h) to give a pink, opaque solution. This solution was then transferred to a 500-mL separatory funnel containing distilled water (150 mL) and EtOAc (200 mL). The organic layer was removed, and the aqueous layer was acidified by the addition of 1 M aqueous HCl (100 mL) and re-extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 2 M aqueous KOH (2 × 150 mL) and saturated aqueous brine (1 × 200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a brown-orange solid (11.3 g, 98%). The crude material was taken up in boiling EtOH (200 mL) and submitted to a hot filtration (Kimwipe), and the volume was reduced to 100 mL. The orange solution was allowed to cool to rt and then −20 °C for 2.5 h, forming small, dark orange crystals. The crystals were collected by Büchner filtration and rinsed with cold (−20 °C) EtOH. The insoluble material from hot filtration above was redissolved in boiling chloroform (100 mL), submitted to a hot filtration, and allowed to cool to rt and then −20 °C for 18 h, in which long pale yellow needles formed. The crystals were collected by Büchner filtration and rinsed with cold (−20 °C) chloroform. Both crystal crops were combined and dried under vacuum (0.1 mmHg) to yield 7.11 g of orange-yellow crystals (61%). Further attempts at recrystallization of the mother liquor were unsuccessful. The isolated material from both recrystallizations matched the spectral characteristics in the previous report.[69] Data for 9,9-dimethyl-2,7-dibromofluorene: mp 172−173 °C (EtOH or $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.55 (s, 1 H, HC(1)), 7.54−7.52 (m, 2 H, HC(1), HC(2)), 7.47 (d, J = 1.7 Hz, 1 H, HC(3)), 7.45 (d, J = 1.7 Hz, 1 H, HC(3)), 1.46 (s, 6 H, H_3C(5)); IR (ATR-FTIR) 2962 (w), 1447 (w), 1398 (w), 1259 (w), 1083 (w), 1059 (w), 1002 (w), 865 (w), 824 (w), 791 (m), 729 (w), 666 (w); LRMS (TOF-AP$^+$) 149.02 (48), 165.07 (12), 176.06 (25), 178.08 (70), 189.07 (18), 191.09 (10), 255.99 (30), 257.99 (35), 272.02 (43), 344.91 (12), 336.90 (26), 349.93 (50), 351.93 (100), 353.93 (50); HRMS (ESI, [M + 1]$^+$) calcd for $C_{15}H_{12}Br_2$ 349.9306, found 349.9305; TLC R_f 0.67 (silica gel, 20:1 hexanes/TBME) [UV].



Preparation of 2-Bromo-7-(hydroxymethyl)-9,9-dimethylfluorene. To a flame-dried, 250-mL, three-necked, round-bottomed flask fitted with a magnetic stir bar, Ar inlet, and internal temperature probe was added 2,7-dibromo-9,9-dimethylfluorene (3.00 g, 8.52 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar, and then THF (42.6 mL) was added to give a pale orange homogeneous solution. The reaction mixture was cooled in a dry ice/acetone bath to an internal temperature of −74 °C. To this solution was added 2.43 M *n*-butyl lithium in hexanes (3.86 mL, 8.95 mmol, 1.05 equiv) dropwise by syringe over 15 min while the internal temperature was maintained below −71 °C to give a deep red solution. The reaction was allowed to stir at −78 °C for an additional 1 h after addition and was then quenched with dimethylformamide (1.33 mL, 17.04 mmol, 2.00 equiv), which resulted in an exotherm to −65 °C. This reaction was warmed to −30 °C over 1 h and then was poured into a rapidly stirred rt 5% aq $NaHCO_3$ solution (140 mL) with loss of the red color to give a heterogeneous yellow solution. This solution was extracted with Et_2O (3 × 60 mL), and the combined organic layer was washed with distilled H_2O (4 × 40 mL) and saturated brine (1 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure (15 mmHg) to give a crude yellow solid (2.52 g, 98%) which was used as is in the next reaction. Data for crude aldehyde: ^{1}H NMR (500 MHz, $CDCl_3$) 10.05 (s, 1 H, OHC(15)), 7.96 (br s, 1 H, HC(1)), 7.87 (dd, J = 7.9, 1.5 Hz, 1 H, HC(4)), 7.82 (d, J = 7.8 Hz, 1 H, HC(3)), 7.65 (d, J = 8.0 Hz, 1 H, HC(8)), 7.61 (d, J = 1.8 Hz, 1 H, HC(10)), 7.51 (dd, J = 8.1, 1.7 Hz, 1 H, HC(7)), 1.51 (s, 6 H, H_3C(14)); ^{13}C NMR (126 MHz, $CDCl_3$) 192.1 (OHC(15)), 157.0 (C(11)), 154.0 (C(13)), 144.6 (C(5), C(6)), 136.8 (C(9)), 135.9 (C(2)), 130.8 (HC(7)), 126.6 (HC(10)), 123.2 (HC(1)), 122.7 (HC(8)), 120.5 (HC(3)), 47.4 (Me_2C(12)), 26.9 (H_3C(14)).

To the 100-mL, single-necked, round-bottomed flask containing crude 2-bromo-7-formyl-9,9-dimethylfluorene (2.42 g, 8.03 mmol, 1.0 equiv) was added a magnetic stir bar and Ar inlet. The flask was evacuated and backfilled with Ar twice, and then EtOH (34 mL) was added. The mixture was stirred to give a heterogeneous, pale yellow solution (starting material is only partially soluble). This flask was cooled in an ice−water bath for 10 min, and then $NaBH_4$ (364.8 mg, 9.64 mmol, 1.2 equiv) was added as a solid in one portion. The reaction was allowed to stir at 0 °C for 1.5 h, at which time the reaction was complete as indicated by TLC (4:1 hexanes/EtOAc, vis/UV). The reaction was quenched carefully at 0 °C with 25 mL of saturated aqueous NH_4Cl to give a cloudy white solution. This mixture was split into two portions and extracted with TBME (3 × 30 mL), and the combined organic layer was washed with saturated brine (1 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure (15 mmHg) and then under high vacuum (0.1 mmHg) at rt for 2 h to give a crude yellow oil (2.676 g). Purification by flash chromatography (SiO_2, 30 mm × 150 mm, Celite dry load, 20 mL fractions, hexanes/EtOAc gradient elution: 10:1 (400 mL) to 4:1 (500 mL) to 3:1 (800 mL)) yielded 2-bromo-7-(hydroxymethyl)-9,9-dimethylfluorene as an off-white/yellow foam (1.56 g, 64% over two steps). This material contained approximately 5% of dehalogenated contaminant that was removed at a later stage in the synthesis. Data for 2-bromo-7-(hydroxymethyl)-9,9-dimethylfluorene: ^{1}H NMR (500 MHz, $CDCl_3$) 7.66 (d, J = 7.7 Hz, 1 H, HC(3)), 7.57 (d, J = 7.6 Hz, 1 H, HC(8)), 7.56 (s, 1 H, HC(1)), 7.46 (dd, J = 1.8, 8.1 Hz, 1 H, HC(7)), 7.44 (s, 1 H, HC(10)), 7.32 (d, J = 7.7 Hz, 1 H, HC(4)), 4.75 (s, 2 H, H_2C(15)), 1.91 (br s, 1 H, OH), 1.48 (s, 6 H, H_3C(14)); ^{13}C NMR (126 MHz, $CDCl_3$) 155.9 (C(13), 153.8 (C(11)), 140.6 (C(2)), 138.0 (C(6)), 137.8 (C(5)), 130.2 (HC(7)), 126.3 (HC(4)), 126.3 (HC(8)), 121.5 (HC(10)), 121.5 (HC(1)), 121.3 (C(9)), 120.3 (HC(3)), 65.7 (C(12)), 47.2 (H_2C(15)), 27.1 (H_3C(14)); IR (ATR-FTIR) 3331 (w), 2956 (w), 2921 (w), 2921 (w), 2858 (w), 1452 (w), 1400 (w), 1257 (w), 1177 (w), 1056 (w), 1003 (w), 815 (m), 740 (w); LRMS (TOF-ES$^+$) 285.0 (50), 287.0 (50), 325.0 (15), 327.0 (15), 393.3 (100), 394.3 (25); HRMS (ESI, [M + 1]$^+$) calcd for $C_{16}H_{15}ONaBr$ 325.0204, found 325.0204; TLC R_f 0.04 (silica gel, 10:1 hexanes/TBME) [UV].



Preparation of 2-Bromo-7-[[(tert-butyldimethylsilyl)oxy]methyl]-9,9-dimethylfluorene. To a flame-dried 250-mL, single-necked, round-bottomed flask fitted with an Ar inlet and stir bar, was added 2-bromo-7-hydroxymethyl-9,9-dimethylfluorene (1.22 g, 4.03 mmol, 1.0 equiv) as a solution in CH_2Cl_2 (15 mL) by cannula. The remaining CH_2Cl_2 (11 mL) was added to the reaction flask, and this mixture was stirred to give a pale yellow solution. To this solution was added *tert*-butyldimethylsilyl chloride (0.81 g, 5.36 mmol, 1.33 equiv) in one portion, and the reaction mixture was cooled in an ice−water bath. At 0 °C were added triethylamine (0.75 mL, 5.36 mmol, 1.33 equiv) and 4-(dimethylamino)pyridine (50 mg, 0.04 mmol, 10 mol %). The reaction was stirred at 0 °C for 15 min and then removed from the ice bath and stirred at rt overnight (18 h). The reaction was complete as determined by TLC (4:1 hexanes/TBME, vis/UV), and the reaction was quenched at rt by the addition of 25 mL of saturated aqueous NH_4Cl solution. The crude reaction mixture was transferred to a 125-mL separatory funnel with CH_2Cl_2 and distilled water. The organic

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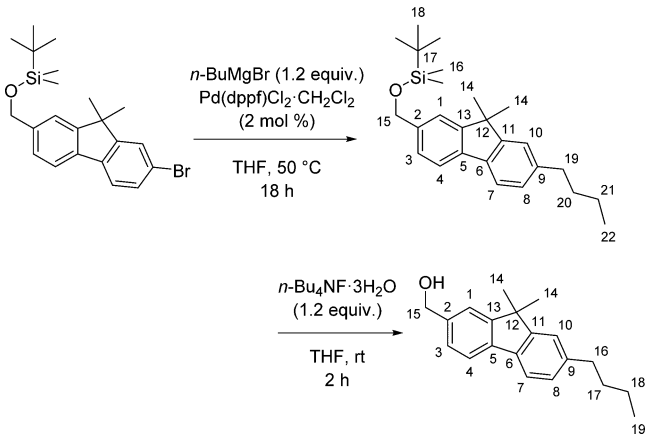
layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with saturated brine solution (1 × 30 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (20 mmHg) and then dried under high vacuum (0.1 mmHg) at rt to give 1.75 g of a pale yellow oil. This crude material was purified by column chromatography (SiO_2, 170 mm × 30 mm, load in hexanes, gradient elution: 100% hexanes (400 mL) to 20:1 hexanes/TBME (400 mL) to 10:1 hexanes/TBME (200 mL), 20 mL fractions (40 total)) to give 2-bromo-7-TBS-(hydroxymethyl)-9,9-dimethylfluorene as a pale yellow oil (1.41 g, 84%) which solidified upon standing at −20 °C. An analytically pure sample was obtained by recrystallization. The low melting white solid was dissolved in a minimum of boiling MeOH (15 mL), subjected to a hot filtration through a preheated glass funnel/Kimwipe into a 50-mL Erlenmeyer flask, rinsed with hot MeOH, and then reduced to an approximate volume of 10 mL. The flask was allowed to cool to rt (no crystallization) and then cooled to −20 °C for 24 h, at which time white crystals formed. The crystals were collected by Büchner filtration, rinsed with ice-cold MeOH, and then dried at rt under reduced pressure (0.1 mmHg). Data for 2-bromo-7-[[(*tert*-butyldimethylsilyl)oxy]methyl]-9,9-dimethylfluorene: mp 58−59 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) 7.64 (d, J = 7.8 Hz, 1 H, HC(4)), 7.55 (d, J = 8.2 Hz, 1 H, HC(8)), 7.54 (d, J = 1.9 Hz, 1 H, HC(10)), 7.44 (dd, J = 8.0, 1.9 Hz, 1H, HC(7)), 7.40 (dd, J = 1.5, 0.7 Hz, 1 H, HC(10)), 7.29 (ddt, J = 7.8, 1.5 0.7 Hz, 1 H, HC(3)), 4.81 (br s, 2 H, $H_2C(15)$), 1.47 (s, 6 H, $H_3C(14)$), 0.96 (s, 9 H, $H_3C(18)$), 0.12 (s, 6 H, $H_3C(16)$); ^{13}C NMR (126 MHz, $CDCl_3$) 155.9 (C(11)), 153.5 (C(13)), 141.4 (C(2)), 138.3 (C(6)), 137.1 (C(5)), 130.1 (HC(7)), 126.3 (HC(8)), 125.3 (HC(3)), 121.4 (HC(10)), 120.9 (C(9)), 120.6 (HC(1)), 119.6 (HC(4)), 65.4 ($H_2C(15)$), 47.1 ($Me_2C(12)$), 27.2 ($H_3C(14)$), 26.1 ($H_3C(18)$), 18.6 ($Me_3C(17)$), −5.0 ($H_3C(16)$); IR (ATR-FTIR) 2956 (w), 2925 (w), 2854 (w), 1454 (w), 1369 (w), 1253 (w), 1110 (m), 878 (w), 834 (m), 821 (m), 776 (m), 740 (w), 669 (w); LRMS (TOF-ES$^+$) 207.1 (43), 285.0 (92), 287.0 (90), 301.0 (12), 303.0 (10), 315.0 (28), 317.0 (28), 337.2 (13), 415.1 (95), 417.1 (100); HRMS (ESI, $[M + 1]^+$) calcd for $C_{22}H_{30}OSiBr$ 415.1093, found 415.1094; TLC R_f 0.71 (silica gel, 10:1 hexanes/TBME) [UV].



Preparation of 7-n-Butyl-2-(hydroxymethyl)-9,9-dimethylfluorene. To a flame-dried, 50-mL, three-neck, round-bottomed flask fitted with a stir bar, Ar inlet, and reflux condenser was added Pd(dppf)Cl_2·CH_2Cl_2 (35.0 mg, 0.04 mmol, 2 mol %). The flask was evacuated and backfilled with Ar twice. To a separate flame-dried, 50-mL, single-necked conical flask with Ar inlet was added 2-bromo-7-TBS-(hydroxymethyl)-9,9-dimethylfluorene (1.00 g, 2.4 mmol, 1.0 equiv). The conical flask was evacuated with backfilled with Ar twice, and then THF (8 mL) was added to give colorless solution. This THF solution was then added to the flask containing the Pd catalyst by cannula, and the conical flask and cannula were rinsed with additional THF (4 mL). The reaction mixture was added to a preheated oil bath (50 °C) and stirred under Ar to give a bright orange, heterogeneous solution. To this heated solution was added 1.87 M *n*-butylmagnesium bromide in diethyl ether (3.60 mL, 2.87 mmol, 1.2 equiv) dropwise by syringe over 10 min. The reaction mixture turned dark purple over the course of the addition. The reaction mixture was then heated at 50 °C for 18 h, at which time full conversion of the starting aryl bromide was observed. Conversion of the starting material was monitored using reverse phase HPLC (Zorbax, 85:15 MeCN/H_2O, 0.6 mL/min, 220 nm, 23 °C, t_{sm} = 6.3 min, t_{pdt} = 12.7 min). The reaction was removed from the oil bath, cooled to 0 °C (ice−water bath), and quenched by slow addition of saturated aqueous NH_4Cl (6 mL), and stirred until gas evolution ceases. The reaction mixture was then transferred to a 125-mL separatory funnel with TBME (30 mL) and distilled water (20 mL). The aqueous layer was separated and extracted with TBME (2 × 20 mL), and the combined organic layer was washed with saturated brine solution (1 × 20 mL), dried over $MgSO_4$, and filtered through a short plug of SiO_2 (2 cm × 3 cm) in TBME to remove the Pd catalyst. This solution was then concentrated under reduced pressure (15 mmHg) and dried under high vacuum at rt (0.1 mmHg) to yield crude 2-*n*-butyl-7-TBS-(hydroxymethyl)-9,9-dimethylfluorene was a brown-purple oil (1.104 g). This crude material was used without further purification. Data for crude TBS-ether: ^{1}H NMR (500 MHz, $CDCl_3$) 7.64 (d, J = 7.7 Hz, 1 H, HC(4)), 7.61 (d, J = 7.7 Hz, 1 H, HC(8)), 7.40 (s, 1 H, HC(1)), 7.27 (dd, J = 6.8, 1.0 Hz, 1 H, HC(3)), 7.24 (s, 1 H, HC(10)), 7.15 (d, J = 7.7 Hz, 1 H, HC(7)), 4.84 (br s, 2 H, $H_2C(15)$), 2.69 (t, J = 7.8 Hz, 2 H, $H_2C(19)$), 1.66 (tdt, J = 9.6, 7.6, 5.8 Hz, 2 H, $H_2C(20)$), 1.48 (s, 6 H, $H_3C(14)$), 1.42 (dd, J = 15.0, 7.4 Hz, 2 H, $H_2C(22)$), 1.02−0.97 (m, 12 H, $H_3C(18)$, $H_3C(22)$), 0.11 (s, 6 H, $H_3C(16)$); ^{13}C NMR (126 MHz, $CDCl_3$) 154.0 (C(11)), 153.9 (C(13)), 142.2 (C(9)), 140.2 (C(2)), 138.4 (C(5)), 136.9 (C(6)), 127.2 (HC(7)), 125.1 (HC(3)), 122.7 (HC(10)), 120.6 (HC(1)), 119.7 (HC(4)), 119.5 (HC(8)), 65.6 ($H_2C(15)$), 46.7 ($Me_2C(12)$), 36.2 ($H_2C(19)$), 34.2 ($H_2C(20)$), 27.3 ($H_3C(14)$), 26.1 ($H_3C(18)$), 22.7 ($H_2C(21)$), 18.6 ($Me_3C(17)$), 14.2 ($H_3C(22)$), −5.0 ($H_3C(16)$).

To the 50-mL, single-necked, round-bottomed flask containing crude 7-*n*-butyl-2-TBS-(hydroxymethyl)-9,9-dimethylfluorene (1.08 g) was added a stir bar and Ar inlet. The flask was evacuated and backfilled with Ar, and then THF (22.3 mL) was added to give a brown-yellow homogeneous solution. To a separate vial was added tetrabutylammonium fluoride trihydrate (1.04 g, 3.29 mmol, 1.2 equiv) within a drybox. This vial was removed from the drybox, and the solid was added immediately to the reaction mixture. The vial was rinsed with THF (0.5 mL), and the reaction was stirred at rt for 2 h, at which time full conversion of the starting material was observed by TLC (4:1 hexanes/EtOAc, vis: UV). The reaction was quenched at rt by the addition of saturated aqueous NH_4Cl (20 mL). The reaction mixture was transferred to a 125-mL separatory funnel with EtOAc (20 mL) and distilled water (10 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layer was washed with brine (1 × 30 mL), dried over Na_2SO_4, filtered (Kimwipe), and concentrated under reduced pressure (15 mmHg) to yield an orange oil (1.24 g). The crude material was adsorbed onto Celite and purified by flash chromatography (SiO_2, 30 mm × 180 mm, dry load with 5% EtOAc in hexanes, 20 mL fractions, gradient elution: 5% EtOAc in hexanes (400 mL) to 10% (2 L) to 20% (500 mL)). Pure 7-*n*-butyl-2-(hydroxymethyl)-9,9-dimethylfluorene eluted first as a purple spot when stained with CAM and eventually coeluted with a small amount of dehalogenated side product which appears as a bright blue spot in CAM. These mixed fractions were collected separately (231 mg). Purified 7-*n*-butyl-2-(hydroxymethyl)-9,9-dimethylfluorene was isolated as a viscous pale yellow oil (0.420 g, 55% over two steps) and used without further purification. An analytical sample was obtained by distillation of a small amount of the purified material using a diffusion pump (Kugelrhor distillation, air bath = 150 °C, 3.2 × 10^{-5} mm Hg). Data for 7-*n*-butyl-2-(hydroxymethyl)-9,9-dimethylfluorene: bp 150 °C (air bath, 3.2 × 10^{-5} mm Hg); ^{1}H NMR (500 MHz, $CDCl_3$) 7.67 (d, J = 7.7 Hz, 1 H, HC(4)), 7.63 (d, J = 7.7 Hz, 1 H, HC(8)), 7.44 (br s, 1 H, HC(1)), 7.31 (dd, J = 7.7, 1.7 Hz, 1 H, HC(3)), 7.25 (br s, 1 H, HC(10)), 7.17 (dd, J = 7.7, 1.7 Hz, 1 H, HC(7)), 4.76 (br s, 2 H, $H_2C(15)$), 2.71 (t, J = 7.9 Hz, 2 H, $H_2C(16)$), 1.83 (br s, 1 H, OH), 1.67 (tt, J = 6.1, 7.9 Hz, 2 H, $H_2C(17)$), 1.49 (s, 6 H, $H_3C(14)$), 1.42 (h, J = 7.4 Hz, 2 H, $H_2C(18)$), 0.97 (t, J = 7.4 Hz, 3 H, $H_3C(19)$); ^{13}C

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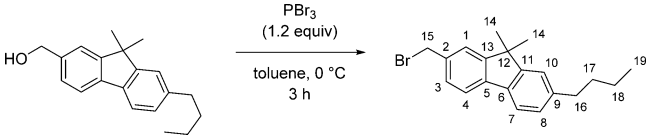
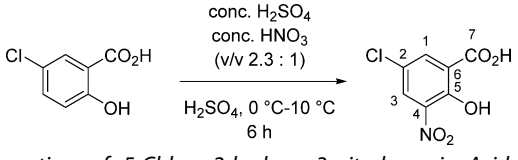
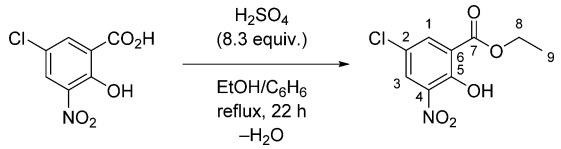
NMR (126 MHz, $CDCl_3$) 154.1 (C(13)), 154.1 (C(11)), 142.5 (C(9)), 139.6 (C(2)), 139.1 (C(5)), 136.5 (C(6)), 127.3 (HC(7)), 126.1 (HC(3)), 122.8 (HC(10)), 121.5 (HC(1)), 119.8 (HC(4)), 119.8 (HC(8)), 65.9 (H_2C(15)), 46.8 (Me_2C(12)), 36.2 (H_2C(16)), 34.1 (H_2C(17)), 27.4 (H_3C(14)), 22.7; IR (ATR-FTIR) 3322 (w), 2956 (m), 2930 (m), 2858 (m), 1614 (w), 1462 (m), 1177 (w), 1108 (w), 909 (m), 815 (m), 730 (m); LRMS (TOF-ES$^+$ w/NaCl) 263.2 (45), 263.4 (18), 303.2 (100), 304.2 (25); HRMS (ESI, $[M + Na]^+$) calcd for $C_{20}H_{24}ONa$ 303.1725, found 303.1731; TLC R_f 0.08 (silica gel, 10:1 hexanes/TBME) [UV]. Anal. Calcd for $C_{20}H_{24}O$ (280.41): C, 85.67; H, 8.63. Found: C, 85.32; H, 8.67.



Preparation of 7-n-Butyl-2-(bromomethyl)-9,9-dimethylfluorene. To a flame-dried, single-necked, 50-mL round-bottomed flask fitted with an Ar inlet and magnetic stir bar was added 7-*n*-butyl-2-(hydroxymethyl)-9,9-dimethylfluorene (280 mg, 1.0 mmol, 1.0 equiv) as a solution in toluene (4 mL) by cannula under Ar. The cannula was rinsed with an additional 1.6 mL of toluene. The colorless, homogeneous solution was cooled in an ice−water bath (I.T. < 1 °C), and phosphorus tribromide (0.11 mL, 1.17 mmol, 1.17 equiv) was added dropwise by syringe over 5 min. The reaction was stirred at 0 °C for 1.5 h and then quenched by pouring into ice-cold saturated Na_2CO_3 solution (100 mL). The reaction mixture was poured into a 250-mL separatory funnel and extracted with dichloromethane (3 × 50 mL). The combined organic layer was washed with distilled water (1 × 50 mL) and saturated brine solution (1 × 50 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to yield 7-*n*-butyl-2-(bromomethyl)-9,9-dimethylfluorene as a thick colorless oil (290 mg, 84%). This material was used without further purification due to instability to column chromatography. An analytical sample was prepared by distillation (air bath = 120 °C, 2.6 × 10^{-5} mm Hg). Data for 7-*n*-butyl-2-(bromomethyl)-9,9-dimethylfluorene: bp 120 °C (air bath, 2.6 × 10^{-5} mm Hg); ^{1}H NMR (500 MHz, $CDCl_3$) 7.64 (d, J = 7.7 Hz, 1 H, HC(3)), 7.62 (d, J = 7.7 Hz, 1 H, HC(8)), 7.44 (br s, 1 H, HC(1)), 7.36 (dd, J = 1.7, 7.8 Hz, 1 H, HC(4)), 7.25 (br s, 1 H, HC(10)), 7.17 (dd, J = 1.6, 7.7 Hz, 1 H, HC(7)), 4.61 (s, 2 H, H_2C(15)), 2.70 (dd, J = 6.7, 9.1 Hz, 2 H, H_2C(16)), 1.66 (p, J = 76 Hz, 2 H, H_2C(17)), 1.49 (s, 6 H, H_3C(14)), 1.41 (h, J = 7.3 Hz, 2 H, H_2C(18)), 0.97 (t, J = 7.3 Hz, 3 H, H_3C(19)); ^{13}C NMR (126 MHz, $CDCl_3$) 154.3 (C(11)), 154.2 (C(13)), 142.9 (C(9)), 139.9 (C(5)), 136.2 (C(2)), 136.2 (C(6)), 128.2 (HC(4)), 127.4 (HC(7)), 123.5 (HC(1)), 122.8 (HC(10)), 120.0 (HC(3)), 120.0 (HC(8)), 46.8 (C(12)), 36.2 (H_2C(16)), 34.6 (H_2C(15)), 34.1 (H_2C(17)), 27.3 (H_3C(14)), 22.7 (H_2C(18)), 14.2 (H_3C(19)); IR (ATR-FTIR) 2956 (m), 2925 (m), 2858 (m), 1614 (w), 1467 (m), 1208 (m), 891 (w), 820 (m), 744 (m), 655 (m), 566 (w), 548 (w); LRMS (EI$^+$, 70 eV) 123.0 (12), 179.9 (20), 205.0 (17), 220.0 (15), 248.0 (12), 263.0 (100), 341.9 (10), 342.9 (10), 342.9 (3), 343.9 (10), 344.9 (3); HRMS (EI, $[M]^+$) calcd for $C_{20}H_{24}Br$, 342.0982, found 342.0981; TLC R_f 0.71 (silica gel, 10:1 hexanes/TBME) [UV]. Anal. Calcd for $C_{20}H_{24}Br$ (343.31): C, 69.97; H, 6.75. Found: C, 70.31; H, 6.78.



Preparation of 5-Chloro-2-hydroxy-3-nitrobenzoic Acid. To a 250-mL, single-neck, round-bottomed flask equipped with a magnetic stir bar and internal temperature probe were added 5-chlorosalicylic acid (10.0 g, 57.95 mmol, 1.0 equiv) and concentrated sulfuric acid (38 mL). The reaction mixture was cooled in an ice−salt water bath (I.T. < 1 °C) and stirred open to air to give a turbid, colorless solution. A 50-mL Erlenmeyer flask containing concentrated (98%) sulfuric acid (15.6 mL) was cooled in an ice−water bath and then treated with concentrated (70%) nitric acid (6.6 mL) dropwise with gentle swirling to give a colorless, nitrating solution. The nitrating solution (10.4 mL) was then added to the reaction mixture dropwise by pipet over 40 min while the internal temperature was maintained below 5 °C. Over the course of addition, the reaction mixture turned from bright yellow to a dark brown. Following complete addition, the cooling bath was removed, a yellow cap was added, and the reaction was stirred at rt for 2.5 h. The reaction mixture still contained starting salicylic acid as determined by TLC analysis (30% EtOH in $CHCl_3$ with 1% AcOH). An additional 3 mL of nitrating solution was added at rt, and the reaction was stirred for an additional 2.5 h, at which time the starting material was completely consumed. The reaction was quenched by pouring into an ice-cold 500-mL Erlenmeyer containing approximately 100 mL of ice to produce a pale yellow precipitate. The quenched heterogeneous mixture was stirred for 15 min at 0 °C, and then the pale yellow precipitate was collected by vacuum filtration through a sintered glass funnel. The filter cake was rinsed generously with ice-cold distilled water to remove any residual acid and then dried on funnel overnight. The crude product was then transferred to a 250-mL single-neck round-bottomed flask and stirred under vacuum (0.1 mmHg) at rt for 3 h to give a free-flowing off-white solid (12.0 g, 95%). This solid was suspended in 200 mL of boiling hexanes to give a yellow slurry. EtOH (10 mL) was added dropwise over which most of the crude material becomes soluble. The insoluble material was allowed to settle, and the solution was subjected to a hot filtration through a Kimwipe. The filtrate was reheated to homogeneity, and the neon yellow solution was allowed to stand at rt undisturbed for 2 h, over which time pale yellow-white needles formed. These crystals were collected by vacuum filtration and rinsed with ice-cold 5% EtOH in hexanes. The mother liquor was subjected to two additional recrystallizations following the same procedure, and all three crystal crops were combined to give 5-chloro-2-hydroxy-3-nitrobenzoic acid (8.44 g, 67%). An analytically pure sample was obtained as follows. The white crystalline compound (440 mg) was taken up in 10 mL of boiling hexanes to give a pale yellow slurry. Boiling EtOH (1 mL) was added dropwise to this solution to give a homogeneous solution, which was submitted to a hot filtration through a preheated glass funnel/Kimwipe into a 50 mL Erlenmeyer flask. To this solution was added an additional 20 mL of hexanes and the solution was reheated to homogeneity. This solution was allowed to cool slowly to rt, over which time white crystals formed. The recrystallization was allowed to stand at rt for 2 h undisturbed, then collected by Büchner filtration and rinsed with an excess of room temperature hexanes. The white crystals were transferred to a oven-dried scintillation vial (previously washed with No-Chromix solution), the crystals were ground with a glass stirring rod, and then dried in a drying pistol over P_2O_5 (dichloromethane) under high vacuum (0.1 mmHg) for 2 h, then dried at rt for an additional 3 h, to give 429 mg, of the fluffy white solid (97% recovery). Data for 5-chloro-2-hydroxy-3-nitrobenzoic acid: mp 163−164 °C (hexanes/EtOH); ^{1}H NMR (500 MHz, CD_3OD) 8.18 (d, J = 2.7 Hz, 1H, HC(3)), 8.16 (d, J = 2.7 Hz, 1H, HC(1)); ^{13}C NMR (126 MHz, CD_3OD) 169.7 (HO_2C(7)), 154.3 (O_2N−C(4)), 138.7 (HO_2CC(6)), 134.4 (HC(3)), 129.7 (HC(1)), 120.9 (ClC(2)), 118.6 (HOC(5)); IR (ATR-FTIR) 3080 (w), 1681 (w), 1526 (w), 1434 (w), 1345 (w), 1233 (m), 1166 (w), 909 (w), 797 (w), 728 (w), 698 (m), 551 (w), 499 (w), 462 (w); LRMS (EI$^+$, 7.3 eV) 67.0 (15), 68.0 (68), 69.0 (27), 98.0 (72), 99.0 (22), 127.0 (66), 142.1 (100), 149.0 (10), 151.1 (8), 176.1 (30), 177.1 (12), 192.1 (10); HRMS (ESI, $[M - 1]^-$) Calcd for $C_7H_3NO_5Cl$, 215.9700; found, 215.9699; TLC R_f 0.12 (silica gel, 70:30 $CHCl_3$/EtOH w/1% AcOH) [UV]. Anal. Calcd for $C_7H_4NO_5Cl$ (217.56): C, 38.65; H, 1.85; N, 6.44. Found: C, 38.44; H, 1.75; N, 6.25.



Preparation of Ethyl 5-Chloro-2-hydroxy-3-nitrobenzoate. To a flame-dried, 500-mL, single-neck, round-bottomed flask fitted with a

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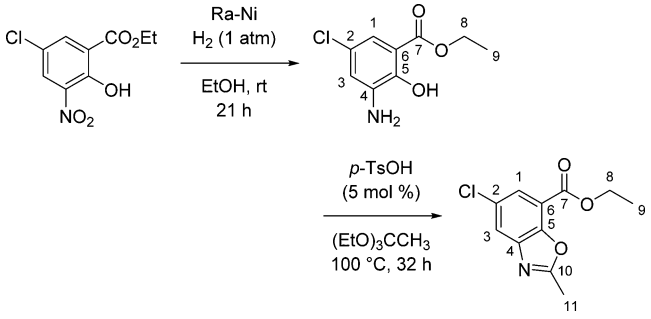
stir bar, reflux condenser, and Dean−Stark trap was added 5-chloro-2-hydroxy-3-nitrobenzoic acid (8.00 g, 36.77 mmol, 1.0 equiv). EtOH (80 mL) was added, and the reaction was stirred at rt to give a homogeneous, neon yellow solution. At rt, concentrated (98%) sulfuric acid (16.2 mL) was added slowly, producing a slight exotherm. Benzene (80 mL) was then added, and the reaction mixture was heated to reflux with azeotropic removal of water (oil bath temperature 78 °C). Periodically, the Dean−Stark trap was emptied, and after 21 h, the reaction was complete by TLC analysis (30% EtOH in $CHCl_3$ with 1% AcOH). The reaction was removed from the oil bath, allowed to cool to rt, and then concentrated to a minimal volume (approximately 20 mL) by rotary evaporation to give a pale yellow slurry. The reaction mixture was transferred to a 500-mL separatory funnel with EtOAc (150 mL), and the solution was neutralized with 5% aqueous $NaHCO_3$ (100 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a pale yellow solid (9.03 g, 100%). Further basic workup (pH > 5) should be avoided due to deprotonation of phenolic residue to give a neon orange solid which is sparingly soluble in most solvents. The crude material was dissolved in a minimum of boiling EtOH (75 mL), submitted to a hot filtration through a Kimwipe into a 250-mL Erlenmeyer, reheated to homogeneity, and allowed to cool to room temperature. The yellow solution was then cooled in an ice−water bath for 30 min to induce crystallization, and then the flask was then cooled to −20 °C overnight. The white starburst crystals were collected by vacuum filtration, rinsed with −20 °C EtOH, and then dried at rt under vacuum (0.1 mmHg) to give a white crystalline solid. An analytically pure sample was obtained by recrystallizing a small portion of the above material. The crystalline material (450 mg) was taken up in a minimum of boiling EtOH (10 mL) to give a homogeneous, bright yellow solution. This solution was filtered through a preheated glass funnel/Kimwipe into a 50 mL Erlenmeyer flask. An addition 15 mL of EtOH was added and the solution was reheated to homogeneity. This solution was allowed to cool to rt slowly, then cooled in an ice−water bath and scratched to induce crystallization. The flask was allowed to stand undisturbed at 0 °C for 2 h, then at −20 °C for 18 h. The shiny white flakes were collected by Büchner filtration, rinsed with an excess of cold (−20 °C) EtOH, and allowed to dry on the filter paper until a free-flowing solid was obtained. The white crystals were transferred to an oven-dried scintillation vial (previously washed with No-Chromix solution), the crystals were ground with a glass stirring rod, and then dried in a drying pistol over P_2O_5 (dichloromethane) under high vacuum (0.1 mmHg) for 3 h, then dried at rt for an additional 2 h, to give 363.4 mg, of the fluffy white solid (81% recovery). Data for ethyl 5-chloro-2-hydroxy-3-nitrobenzoate: mp 64−65 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) 12.02 (s, 1H, OH), 8.14 (d, J = 2.7 Hz, 1H, HC(3)), 8.10 (d, J = 2.7 Hz, 1H, HC(1)), 4.49 (q, J = 7.1 Hz, 2H, $H_2C(8)$), 1.46 (t, J = 7.1 Hz, 3H, $H_3C(9)$); ^{13}C (126 MHz, $CDCl_3$) 168.1 (O═C(7)), 154.4 (O_2N−C(4)), 138.4 ($EtO_2CC(6)$), 135.2 (HC(3)), 131.1 (HC(1)), 123.5 (ClC(2)), 117.0 (HOC(5)), 63.3 ($H_2C(8)$), 14.2 ($H_3C(9)$); IR (ATR-FTIR) 3088 (w), 1670 (m), 1585 (w), 1535 (m), 1443 (m), 1406 (w), 1382 (w), 1344 (m), 1321 (m), 1249 (s), 1185 (m), 1171 (m), 1116 (w), 1018 (m), 936 (w), 906 (w), 894 (w), 868 (w), 816 9w), 796 (s), 760 (w), 722 (s), 553 (w); LRMS (TOF-AP$^+$) 140.97 (10), 198.97 (15), 199.98 (100), 201. 97 (30), 216.98 (15), 245.01 (15), 246.02 (10); HRMS (ESI, [M − 1]$^-$) Calcd for $C_9H_7NO_5Cl$, 244.0013; found, 244.0011; TLC R_f 0.36 (silica gel, 4:1 hexanes/EtOAc) [UV, by eye]. Anal. Calcd for $C_9H_8NO_5Cl$ (245.62): C, 44.01; H, 3.28; N, 5.70. Found: C, 43.83; H, 3.15; N, 5.57.



Preparation of Ethyl 5-Chloro-2-methylbenzo[d]oxazole-7-carboxylate. To a flame-dried, 250-mL, round-bottomed, single-neck flask fitted with a septum and magnetic stir bar was added ethyl 5-chloro-2-hydroxy-3-nitrobenzoate (7.72 g, 31.43 mmol, 1.0 equiv). The flask was evacuated and backfilled with Ar, EtOH (93 mL) was added, and the reaction mixture was stirred under Ar at rt to give a homogeneous, bright yellow solution. Three spatula tips of Raney nickel (approximately 1.0 g total) were added and rinsed off of the slides with EtOH (7 mL) to give a heterogeneous, green solution. The reaction system was removed from Ar, and the headspace was purged with two balloons of H_2 (g), over which time the reaction turns slightly yellow. The balloon was refilled and the system was sealed and stirred at rt for 18 h. Initially, the reaction mixture turned red but then ended as army green. The balloon was refilled the next morning, and the reaction was stirred for an addition 6 h, over which time the balloon pressure did not appear to change. The headspace was then cleared of hydrogen gas by purging with Ar for 15 min. The reaction mixture was filtered through Celite using an excess of EtOAc (500 mL), taking care to not allow the Raney nickel to become dry. The filtrate was concentrated by rotary evaporation to yield a yellow-green sludge. This solid was redissolved in TBME (100 mL) and precipitated with hexanes (200 mL). Concentration with successive precipitation with hexanes yielded ethyl 3-amino-5-chloro-2-hydroxybenzoate as a workable mustard-yellow solid (6.68 g, 99%). This material was stored under Ar and used immediately in the next reaction. Data for crude aminophenol: mp 48−52 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 10.63 (br s, 1 H, OH), 6.90 (d, J = 2.6 Hz, 1 H, HC(1)), 6.82 (d, J = 2.6 Hz, 1 H, HC(3)), 5.34 (br s, 2 H, NH_2), 4.33 (q, J = 7.1 Hz, 2 H, $H_2C(8)$), 1.32 (t, J = 7.1 Hz, 3 H, $H_3C(9)$); ^{13}C NMR (126 MHz, $CDCl_3$) 169.0 ($EtO_2C(7)$), 147.1 (EtO_2C−C(6)), 139.7 (Cl−C(2)), 123.0 (H_2N−C(4)), 116.6 (HC(1)), 113.8 (HC(3)), 112.0 (HO-C(5)), 61.6 ($H_2C(8)$), 13.8 ($H_3C(9)$). IR (ATR-FTIR) 3435 (s), 3322 (s), 1675 (m), 1637 (s), 1474 (m), 1397 (s), 1297 (m), 1278 (m), 1221 (m), 1184 (m), 1114 (s), 1035 (m), 841 (s), 782 (m), 725 (m), 688 (m), 489 (m); LRMS (TOF-AP$^+$) 114.01 (12), 142.01 (32), 144.00 (10), 168.99 (17), 170.00 (100), 171.99 (31), 216.04 (10); HRMS (ESI, [M + 1]$^+$) calcd for $C_9H_{10}NO_3Cl$ 216.0427, found 216.0424.

To the 500-mL round-bottomed flask containing crude ethyl 3-amino-5-chloro-2-hydroxybenzoate (6.50 g, 30.14 mmol, 1.0 equiv) was added *p*-toluenesulfonic acid (260 mg, 5 mol %). The flask was fitted with a magnetic stir bar and Ar inlet, evacuated, and backfilled with Ar. Triethyl orthoacetate (55 mL, 10 equiv) was added, and the solution was stirred at rt to give a brown solution. The flask was fitted with a reflux condenser and then added to a preheated oil bath (oil bath temp = 100 °C). The reaction was stirred at 100 °C for 32 h and then allowed to cool to rt. The solvent was then partially removed by rotary evaporation, and the mixture was stirred at 40 °C under high vacuum (0.1 mmHg) with a dry ice condenser trap to remove residual triethyl orthoacetate to give a brown solid (7.81 g, >100%). The crude material was purified by flash chromatography (SiO_2, 40 mm × 200 mm, 400 mL forecut then 25 mL fractions (48 total), loaded on Celite, eluent: 15% EtOAc in hexanes (2 L) to 33% EtOAc in hexanes (300 mL)) yields ethyl 5-chloro-2-methylbenzo[*d*]oxazole-7-carboxylate as a white solid (4.84 g, 67% over 2 steps). Data for ethyl 5-chloro-2-methylbenzo[*d*]oxazole-7-carboxylate: mp 64−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.90 (d, J = 2.1 Hz, 1 H, HC(1)), 7.80 (d, J = 2.1 Hz, 1 H, HC(3)), 4.47 (q, J = 7.1 Hz, 2 H, $H_2C(8)$), 2.71 (s, 3 H, $H_3C(11)$), 1.45 (t, J = 7.1 Hz, 3 H, $H_3C(9)$); ^{13}C NMR (126 MHz, $CDCl_3$) 166.6

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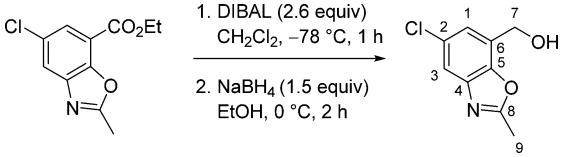
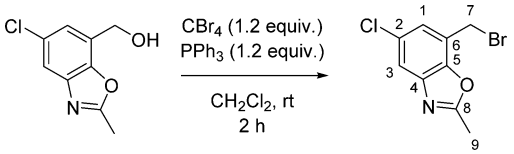
(H_3CNO-C(10)), 163.2 (EtO_2C(7)), 148.8 (EtO_2C–C(6)), 144.2 (C(4)), 129.6 (Cl–C(2)), 126.5 (HC(3)), 124.0 (HC(1)), 115.7 (C(5)), 61.9 (H_2C(8)), 14.8 (H_3C(11)), 14.4 (H_3C(9)). IR (ATR-FTIR) 3061 (w), 1720 (m), 1624 (w), 1577 (w), 1461 (w), 1414 (w), 1331 (w), 1294 (m), 1236 (m), 1208 (w), 1162 (m), 1115 (w), 1044 (m), 1015 (w), 997 (w), 919 (m), 896 (m), 885 (w), 864 (w), 834 (m), 781 (m), 746 (m), 659 (w), 642 (w), 592 (w); LRMS (TOF-AP$^+$) 166.0 (12), 168.0 (8), 194.0 (100), 196.0 (30), 211.0 (18), 212.0 (28), 214.0 (10), 239.0 (23), 240.0 (75), 242.0 (28); HRMS (ESI, [M + 1]$^+$) calcd for $C_{11}H_{10}NO_3Cl$ 239.0349, found 239.0349; TLC R_f 0.31 (silica gel, 4:1 hexanes/EtOAc) [UV]. Anal. Calcd for $C_{11}H_{10}NO_3Cl$ (239.66): C, 55.13; H, 4.21; N, 5.84. Found: C, 54.87; H, 4.11; N, 5.83.



Preparation of 5-Chloro-7-(hydroxymethyl)-2-methylbenzo[d]-oxazole. To a flame-dried, 250-mL, three-neck round-bottomed flask fitted with an Ar inlet, internal temperature probe, and magnetic stir bar was added ethyl 5-chlorobenzo[*d*]oxazole-7-carboxylate (2.50 g, 10.43 mmol, 1.0 equiv) under a stream of Ar. The solid material was taken up in dichloromethane (70 mL) and cooled in a dry ice/acetone bath (I.T. = −79 °C). To this solution was added 1.0 M DIBAL-H in hexanes (27.1 mL, 2.6 equiv) dropwise over 15 min while the internal temperature was maintained below −74 °C. The reaction was stirred at −78 °C for 45 min, and then the reaction was quenched by the addition of EtOAc (4.1 mL) for 1 h followed by the addition of saturated Rochelle's salt solution (20 mL). The reaction mixture was transferred 250-mL separatory funnel with dichloromethane (30 mL) and saturated brine (20 mL). The resultant emulsion was extracted with EtOAc (4 × 50 mL), dried over Na_2SO_4, filtered through Celite, and concentrated by rotary evaporation to yield a crude red-orange solid that was used directly in the next step.

A 100-mL, round-bottomed flask containing the crude material from the previous step was fitted with an Ar inlet and magnetic stir bar, evacuated, and backfilled with Ar. To this flask was added EtOH (31 mL), and the reaction was cooled in an ice–water bath. Sodium borohydride (177.6 mg, 4.70 mmol, 1.5 equiv) was added in a single portion, and the reaction was stirred at 0 °C for 2 h and then quenched by the slow addition of saturated aqueous NH_4Cl (30 mL). The reaction mixture was concentrated by rotary evaporation to remove the majority of the EtOH and then transferred to a 60-mL separatory funnel with 20 mL of EtOAc. The aqueous layer was extracted with EtOAc (3 × 15 mL) and dichloromethane (2 × 20 mL). The crude organic mixture was dried over Na_2SO_4, filtered through Celite, concentrated, and dried under vacuum (0.1 mmHg) to give the crude material as a brown solid. Purification by flash chromatography (SiO_2, 30 mm × 210 mm, 10 mL fractions, dry load on Celite, hexanes/EtOAc gradient elution (15:1 (200 mL) to 10:1 (200 mL) to 4:1 (500 mL) to 2:1) yielded 5-chloro-7-(hydroxymethyl)-2-methylbenzo[*d*]oxazole as a pale pink solid (630 mg, 30% over 2 steps). . A small portion (120 mg) was dissolved in a minimum of boiling EtOH (15 mL), subjected to a hot filtration (Kimwipe), and reduced to a volume of approximately 10 mL. This solution was allowed to cool to room temperature and was then cooled in an ice–water bath to initiate crystallization. Upon crystal formation, the flask was cooled to −20 °C for 18 h. The slightly pink crystals were collected by Büchner filtration, rinsed with cold −20 °C) ethanol and then ice-cold pentane. The solid was collected in a No-Chromix washed scintillation vial and dried under high vacuum (0.1 mmHg) overnight at rt to yield 7-(hydroxymethyl)-5-chloro-2-methylbenzo-[*d*]oxazole was a pale pink powder. Data for 5-chloro-7-(hydroxymethyl)-2-methylbenzo[*d*]oxazole: mp 141–142 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) 7.52 (d, J = 2.1 Hz, 1 H, HC(3)), 7.32 (d, J = 2.1 Hz, 1 H, HC(1)), 4.92 (s, 2 H, H_2C(7)), 2.63 (s, 3 H, H_3C(9)), 2.46 (br s, 1 H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) 165.3 (C(8)), 147.2 (C(5)), 142.5 (C(4)), 129.8 (C(2)), 125.1 (C(6)), 123.5 (HC(1)), 118.6 (HC(3)), 59.7 (H_2C(7)), 14.7 (H_3C(9)); IR (ATR-FTIR) 3336 (w), 2872 (w), 2833 (w), 1571 (w), 1410 (m), 1374 (w), 1311 (w), 1280 (m), 1206 (w), 1170 (m), 1102 (m), 1076 (w), 1025 (w), 1002 (m), 932 (m), 890 (w), 883 (w), 860 (m), 824 (m), 702 (w), 660 (m), 601 (w), 546 (m); LRMS (EI$^+$, 70 eV) 62.9 (17), 75.0 (16), 92.0 (20), 126.0 (30), 134.0 (17), 154.9 (16), 162.0 (47), 167.9 (25), 1799 (32), 196.9 (100), 198.9 (30); TLC R_f 0.14 (silica gel, 3:1 hexanes/EtOAc) [UV]. Anal. Calcd for $C_9H_8NO_2Cl$ (197.62): C, 54.70; H, 4.08; N, 7.09. Found: C, 54.62; H, 4.02; N, 6.92.



Preparation of 7-(Bromomethyl)-5-chloro-2-methylbenzo[d]-oxazole. To a flame-dried, 25-mL Schlenk flask fitted with a septum and stir bar were added 7-(hydroxymethyl)-5-chloro-2-methylbenzo-[*d*]oxazole (200 mg, 1.01 mmol, 1.0 equiv) and carbon tetrabromide (402.0 mg, 1.21 mmol, 1.2 equiv). The flask was evacuated and backfilled with Ar twice, then CH_2Cl_2 (14.4 mL) was added and the reaction mixture was stirred to give a dark pink solution. To this mixture was then added triphenylphosphine (318.5 mg, 1.21 mmol, 1.2 equiv) at rt, and then reaction mixture immediate lost its pink color and turned yellow. The reaction was stirred rt for 2 h, after which time the reaction was complete as indicated by TLC (3:1 hexanes/EtOAc, vis: UV). The reaction mixture was then transferred to a 250-mL, round-bottomed flask, Celite was added, and the crude material was absorbed onto Celite using rotary evaporation (20 mmHg) for immediate purification by column chromatography. The crude material was purified by flash chromatography (SiO_2, 25 mm × 130 mm, dry load, equilibration with hexanes, 10 mL fractions, elution: 100% hexanes (150 mL forerun), then 4:1 hexanes/EtOAc (500 mL, 33 fractions total)) to give 7-(bromomethyl)-5-chloro-2-methylbenzo-[*d*]oxazole as a white solid (238.3 mg, 90%). An analytically pure sample was obtained by recrystallization. A small portion (183 mg) was dissolved in a minimum of boiling 2-propanol (20 mL), subjected to a hot filtration (Kimwipe), and reduced to a volume of approximately 15 mL. This solution was allowed to cool to room temperature and was then cooled in an ice–water bath to initiate crystallization. Upon crystal formation, the flask was cooled to −20 °C for 5 h. The white crystals were collected by Büchner filtration and rinsed with ice-cold 2-propanol and then ice-cold pentane. The solid was collected in a No-Chromix washed scintillation vial and dried under high vacuum (0.1 mmHg) overnight at rt to yield 7-(bromomethyl)-5-chloro-2-methylbenzo[*d*]oxazole as a white powder (50.7 mg, 28% recovery). Data for 7-(bromomethyl)-5-chloro-2-methylbenzo[*d*]oxazole: mp 98–99 °C (*i*-PrOH); ^{1}H NMR (500 MHz, $CDCl_3$) 7.58 (d, J = 2.0 Hz, 1 H, HC(3)), 7.31 (d, J = 2.0 Hz, 1 H, HC(1)), 4.64 (s, 2 H, H_2C(7)), 2.68 (s, 3 H, H_3C(9)); ^{13}C NMR (126 MHz, $CDCl_3$) 165.4 (C(8)), 147.5 (C(5)), 142.9 (C(4)), 129.6 (C(2)), 125.4 (HC(1)), 121.7 ((C(6)), 119.4 (HC(3)), 25.2 (H_2C(7)), 14.7 (H_3C(9)). IR (ATR-FTIR) 3040 (w), 2981 (w), 1572 (w), 1406 (w), 1276 (w), 1222 (w), 1182 (w), 1083 (w), 926 (w), 894 (w), 894 (w), 858 (m), 818 (m), 764 (w), 670 (w), 571 (m), 513 (w); LRMS (EI, 70 eV) 75.0 (50), 110.9 (22), 138.9 (20), 179.9 (100), 181.9 (80), 258.8 (20), 260.8 (28); TLC R_f 0.22 (silica gel, 10:1 hexanes/EtOAc) [UV]. Anal. Calcd for $C_9H_7NOClBr$ (260.52): C, 41.49; H, 2.71; N, 5.38. Found: C, 41.35; H, 2.62; N, 5.18.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01759.

Additional experiments with other substrate classes and studies on catalyst inactivation in the rearrangement of 2-(allyloxy)-1-tetralone; ^{1}H, ^{13}C, and ^{19}F NMR spectra of

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all described compounds along with CSP-HPLC chromatograms of the rearrangement products (PDF)

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Notes

The authors declare no competing financial interest.

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