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Synthesis of Acyclic Ketones by Catalytic, Bidirectional Homologation of Formaldehyde with Nonstabilized Diazoalkanes. Application of a Chiral Diazomethyl(pyrrolidine) in Total Syntheses of *Erythroxylon* Alkaloids

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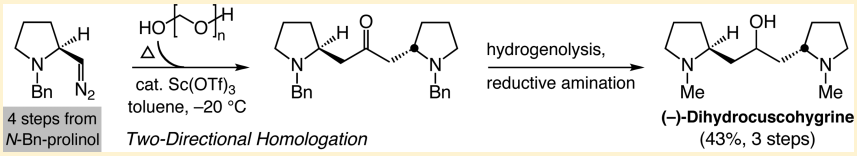
Supporting Information



ABSTRACT: This work offers a catalytic approach to convergent ketone assembly based upon formal and tandem C−H insertion of diazoalkanes in the presence of limiting amounts of monomeric formaldehyde, which is easily generated as a gas by thermolysis of the inexpensive and abundant paraformaldehyde (~30 USD/kg). The method forms di-, tri-, and even tetra-substituted acetones with high efficiency, and it has streamlined a synthesis of (−)-dihydrocuscohygrine in which the absolute stereochemistry of a proline-based starting material is preserved. Assisted by the advent of new protocols for hydrazone oxidation, we also provide full details on handling non-carbonyl-stabilized diazo compounds.

INTRODUCTION

Nucleophilic attack on the carbonyl group remains a standard practice for building C−C bonds. Acyclic ketones, for instance, are routinely prepared by organometal addition and reoxidation. Methods that render the event catalytic in a metal and do not require later readjustment of the oxidation state at the electrophilic carbon are highly desirable. One transformation with these features is the Lewis-acid-catalyzed Roskamp synthesis of β-keto esters from alkyl diazoacetates and aldehydes,[1−3] and a substituted asymmetric variant was recently reported.[4] A reliance on diazoacetate nucleophiles, however, brings limitations to the types of products one can prepare. α-Alkyl-β-keto esters give simple alkanones upon hydrolysis and decarboxylation, but not those with a stereogenic center at the α or α' carbon.

In an effort to uncover general and direct strategies for preparing substituted carbonyl compounds, our laboratory is exploring the use of non-carbonyl-stabilized[5−7] diazoalkanes[8−10] (**a**) as carbon nucleophiles for organic synthesis. As shown in Scheme 1, we have developed catalytic entries to both α-chiral cyclic (**b**) and acyclic ketones (**c**) from cycloalkanone and aldehyde electrophiles, respectively.[11−13] More recently, we recorded the first examples of enantioselective medium ring aryl ketone synthesis by ligating bis- and tris(oxazolines) to the $Sc(OTf)_3$ catalyst in situ.[14,15] The mild diazoalkane−carbonyl homologation reaction[16−18] offers the strategic benefit of a ring expansion or chain extension, giving two new bonds to carbon with dinitrogen as the only stoichiometric byproduct.

As shown herein, the substituted diazomethanes (**a**) can be readily prepared from the corresponding aldehyde or ketone. This suggests that iterative applications of diazoalkane−carbonyl homologation can lead to even greater product diversity. For those carbonyl compounds that cannot be purchased or easily synthesized by alternative routes, some permutations on structure may be harder to derive from simple pairings of diazoalkane and acceptor. In a move toward full modularity, we considered using paraformaldehyde—an inexpensive and widely available carbon source—as a means to prepare any starting material required for the methodology. On the basis of symmetry present in several small natural products and pharmaceutical agents (see Chart 1),[19−24] we chose to begin our investigation by studying the catalysis of double[25−28] diazoalkyl carbon insertion events with formaldehyde as a 1-C feedstock (**a**→**d**, Scheme 1). In this article, we report efficient access to a number of materials- and biologically relevant ketones that were formerly unknown or quite difficult to prepare. Given pervasive concerns about the toxicity and instability of diazo compounds in general, we also

Scheme 1. Varied Strategies for Ketone Synthesis by the Diazoalkane−Carbonyl Homologation Reaction

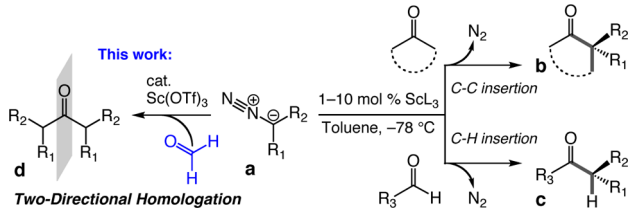


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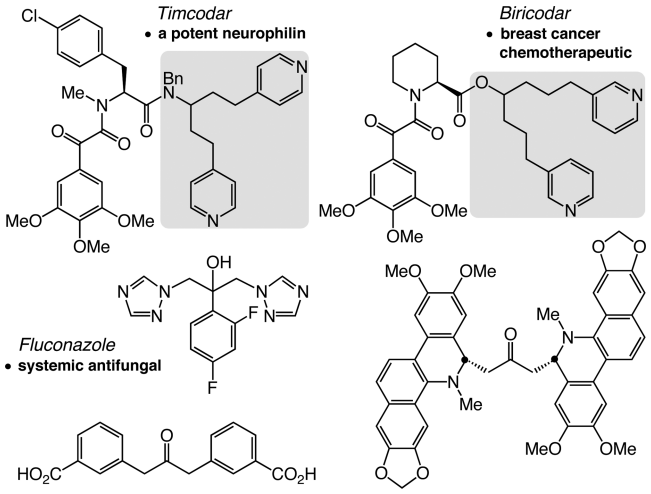
Chart 1. Synthetic and Naturally Occurring Medicinal Agents for Which a Symmetrical 1,3-Disubstituted Propanone Is a Key Structural Feature



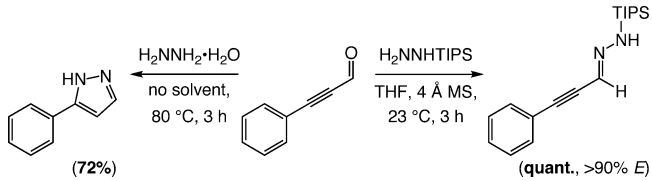
disclose procedures for their safe manipulation as pure, low-temperature organic solutions.

RESULTS AND DISCUSSION

At the outset, our program benefited from three outstanding protocols for nonstabilized diazoalkane synthesis,[29−31] all of which rely on oxidation of the corresponding hydrazone. The most recent, discovered by Brewer, involves dehydrogenation with the Swern reagent.[29] Under optimal conditions of solvent and stoichiometry, pure monoaryl, diaryl, and mixed alkyl−aryl diazomethanes are obtained in high yield by simple filtration of triethylammonium chloride from the reaction mixture. With the exception of *p*-methoxyphenyldiazomethane (**19b**), all aryl and heteroaryl nucleophiles reported herein were synthesized by Brewer's approach directly from unprotected hydrazones. Regrettably, this entry is less effective for mono- and dialkyl diazomethanes, perhaps because of lability in the presence of dimethyl sulfide, a nucleophilic coproduct of the oxidation. It is here, however, that alternative methods offer a solution. Myers has oxidized *N*-*tert*-butyldimethylsilylhydrazones with (difluoroiodo)-benzene as a means to furnish diazoalkanes in situ for acid esterification reactions that are wide in scope.[30] This clever application of the bulky *N*-silyl group renders the intermediate hydrazones bench-stable and shields them against dimerization to the corresponding azines.[32] A third innovation provided by Shechter[31] concerns $Pb(OAc)_4$/tetramethylguanidine/DMF as a reagent trio for hydrazone oxidation beneficial for another reason: the choice of DMF as cosolvent permits clean and near quantitative extraction of the diazo compound from the reaction mixture upon addition of cold hexane or pentane. Anticipating the great advantage that high-purity diazoalkane solutions would offer in the context of reaction development and catalyst discovery, we captured the essential features in each of the latter two methods to develop a "hybrid" protocol for preparative access to the more challenging aliphatic and α,β-unsaturated nucleophiles.

Time and much experimentation point to triisopropylsilylhydrazine[33] as a superior reagent for initial condensation with the ketone or aldehyde. Propargylic carbonyls perhaps best illustrate this fact since they are especially prone to Michael addition and subsequent heterocyclization. If 3-phenylpropionaldehyde is exposed to standard conditions for hydrazone formation (excess hydrazine hydrate, no solvent, 80 °C), 5-phenyl-1*H*-pyrazole can be isolated in an unoptimized 72% yield by simple extraction (Scheme 2). In stark contrast, mild treatment

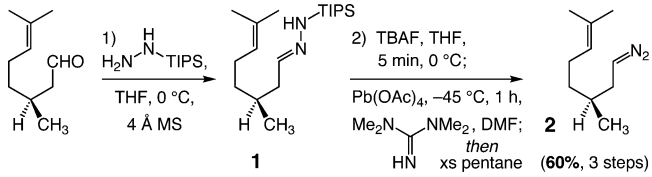
Scheme 2. Divergent Reaction Outcomes in Condensation with Distinct Hydrazine Reagents



with $TIPSNHNH_2$ and 4 Å molecular sieves (THF, 0 °C) affords the target TIPS-hydrazone in quantitative yield, and it can be stored indefinitely below 4 °C under nitrogen. Additional attributes of the monosilyl hydrazine include the fact that (1) it is readily synthesized and distilled in quantity from a mixture triisopropylsilyl chloride and hydrazine[33] and (2) compared to bis(*tert*-butyldimethylsilyl)hydrazine,[30,32] it removes the need for Lewis acid catalysis of the condensation and prevents coproduction of a high molecular weight silanol that must be removed from the sample by prolonged warming under high vacuum.

Further optimization of the carbonyl-to-diazo interchange was carried out with (*S*)-citronellal as a model aliphatic aldehyde (Scheme 3). Treatment with $TIPSNHNH_2$ (1 equiv, THF,

Scheme 3. Efficient Two-Pot Diazoalkane Synthesis from (*S*)-Citronellal



23 °C, 4 Å MS) gave rapid conversion to silylhydrazone **1**, albeit with 5−8% contamination by azine (^{1}H NMR analysis). The impurity can derive from adventitious desilylation[32] of the reagent by the water of condensation. Azine formation is avoided by cooling the mixture (0 °C), switching to pulverized or powdered 4 Å sieves, and adding the reagent slowly (2−4 h, syringe pump) to better control release of water during the reaction. With these modifications, **1** is obtained in >98% yield and purity by filtration and solvent removal. The blocking group is then cleaved by exposure to a commercial solution of TBAF (THF, 0 °C, 5 min), and after a solvent switch (to 0.1 M DMF/tetramethylguanidine), the free hydrazone is treated with 1.1 equiv of oxidant[34] at −45 °C. Subsequent washing of the mixture with three equal-volume portions of cold pentane and siphoning[31] of the organic layers by syringe gives a bright yellow hydrocarbon extract laden with **2**. After washing the solution with 30% KOH at −30 °C to remove any traces of DMF in the extract, the diazoalkane is directly titrated for use or redissolved in a less volatile solvent (e.g., toluene) for storage and dispensing as a stock solution. The 60% yield reported here corresponds to purified (*S*)-citronellal benzoyl ester—obtained by acidic quench of an aliquot (benzoic acid, THF, −45 °C),

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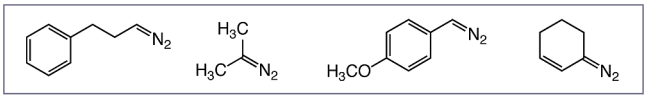
aqueous workup, and chromatography. The yield is a conservative estimate of the preparative efficiency for three distinct operations (four steps total, the first two of which are effected without purification).

The lower diazoalkanes are acutely toxic, explosive gases at room temperature.[35,36] Indeed, this was the principal deterrent to industrial use of diazomethane for almost a century despite its wide and demonstrated utility.[37] However, recent developments allow for diazomethane production at levels of 50−60 metric tons per year.[38] Furthermore, anecdotal evidence suggests that nearly[39] all diazomethane explosions have occurred during its solvent-free distillation, and controlled detonation studies confirm that the hazard is a close function of the reagent's volatility.[38] Substituents at the diazoalkyl carbon atom add molecular weight and stability, and the protocol in Scheme 3 has now safely been applied to a wide range of nonvolatile derivatives that are brightly colored viscous oils or crystalline solids at or below 23 °C (Figure 1). Importantly, the two-pot



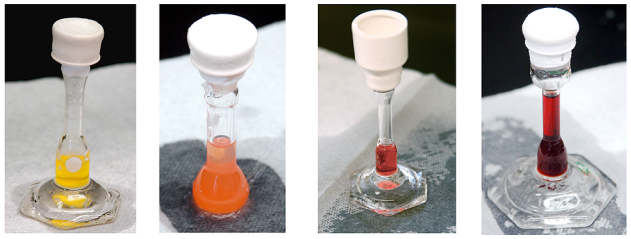
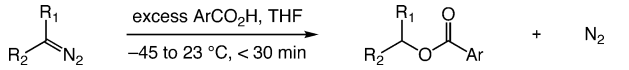


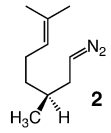
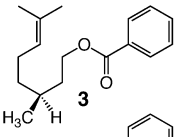
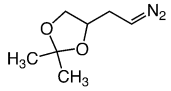
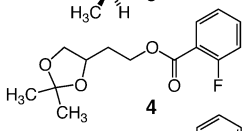
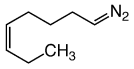
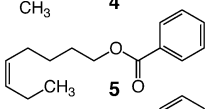
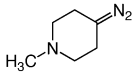
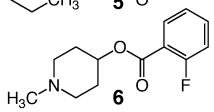
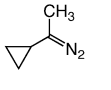
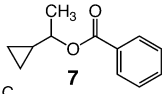
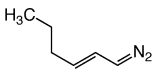
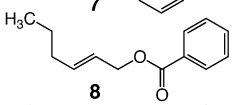
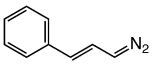
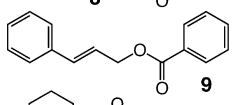
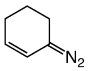
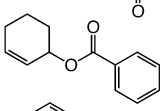
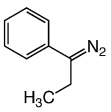
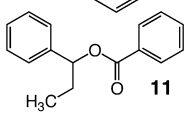
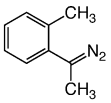
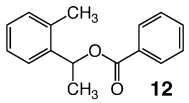
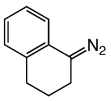
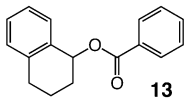
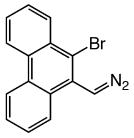
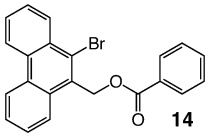
Figure 1. Toluene stock solutions of substituted diazomethanes show longevity upon prolonged storage at or below −20 °C and are readily assayed for the active nucleophile by esterification with benzoic acid. Alkyldiazoalkanes are yellow to orange in color; conjugated species are deep red or violet in comparison.

sequence does not require isolation, purification, or even warming of the potentially hazardous diazo compounds. All required manipulations, including titration, are carried out in solution at low temperature. Diazoalkane **2** has characteristic signals in both its ^{1}H NMR (δ 3.33 ppm, triplet, J = 6.4 Hz) and IR (2025 cm^{-1}) spectra. Regarding longevity in solution, the half-life of **2** is approximately 18 h at 23 °C in benchtop $CDCl_3$. Prolonged stability can be achieved with recourse to a basic additive such as Et_3N, and no measurable drop in titer is observed for solutions of **2** prepared from rigorously air-free, purified solvent. A control reaction with phenyldiazomethane (undertaken to preclude protic catalysis of homologation by hydrates of $Sc(OTf)_3$) shows that in the presence of 1 mol % of TfOH, the primary byproduct is stilbene (∼1:1 *E*:*Z*). By contrast, the main pathway for decomposition with 1 mol % of $Sc(OTf)_3$ (in the absence of a carboxylic acid or carbonyl electrophile) is azine formation, for which there is ample precedent.[40]

The aforementioned quench with benzoic acid serves to accurately titrate any given stock solution prior to its use in a catalytic homologation reaction. It also permits a quantitative assessment of hydrazone synthesis and oxidation efficiencies across a broad range of carbonyl precursors. Table 1 provides representative results for small-scale benzoylations of stock solution aliquots; yields correspond to chromatographically pure ester and are based on the starting ketone or aldehyde.

Table 1. Diazoalkane Benzoylations Secure the Active Titers in Solution



entry	diazoalkane	esterification product	yield (%)[a]
1			60
2			41
3			42
4			37
5			44
6			52
7			59
8			66
9			88[b]
10			82[b]
11			80[b]
12			81[b]

[a]Four-step yield for chromatographically pure benzoate based on the starting ketone or aldehyde (TIPS-hydrazone formation, desilylation, Pb(IV) oxidation/extraction, and esterification). [b]Three-step yield for pure ester by oxidation of the free hydrazone with the Swern reagent.

Some critical ramifications of this data set include the following: (1) Aliphatic mono- and disubstituted diazomethanes are obtained in moderate four-step yields that are routinely lower than their aryl and α,β-unsaturated counterparts (entries 1−5). This trend derives from their heightened sensitivity relative to vinylic examples (entries 6−8) and mechanical losses implicit to their isolation from DMF/pentane bilayers. (2) Good to excellent esterification yields are observed for both terminal and internal aryl diazomethanes (entries 9−12) because of the

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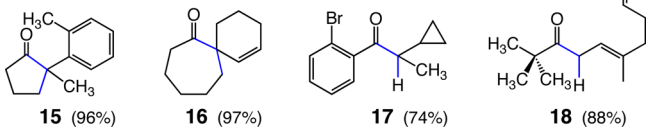
simplicity of Brewer's Swern dehydrogenation[29] method and the universally robust nature of benzylic hydrazones. Here, the overall step count is necessarily lower since temporary *N*-silyl protection of the hydrazone is not needed. (3) The time investment in running an ester synthesis and purifying the reaction mixture—just for the sake of knowing with certainty the active nucleophilic titer—can be dramatically reduced by choosing 2-fluorobenzoic acid for the formal OH insertion. In results communicated previously,[41] our group has devised a convenient ^{19}F NMR-based method that requires <15 min of experimental time and can be performed with micromolar quantities of diazoalkane. A key advantage to the procedure is that conversion, and ultimately diazoalkane concentration, is calculated based on integration of the only two observable ^{19}F signals. Attempts to apply ^{1}H NMR spectroscopy to other substituted benzoic acid derivatives is often successful, but it does not prove to be a universal solution because of problems with overlapping resonances. To conclude, two of the esters in Table 1 (entries 2 and 4) are *ortho*-fluorobenzoates that served to corroborate yields obtained with our more rapid and direct assay based on quantitative ^{19}F NMR spectroscopy.[41]

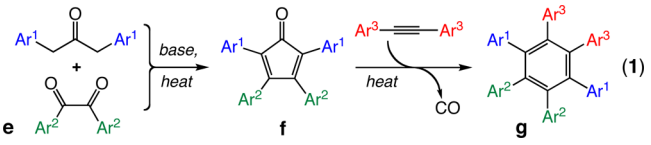
An even greater benefit to practicality could follow work aimed at consuming the nucleophiles the instant they are produced by the application of flow[42,43] or in situ[5,30] techniques. Nonetheless, we have been fortunate to identify inexpensive scandium(III) salts as uniquely effective catalysts for diazoalkane–carbonyl homologation, a discovery that may not have been possible without access to high-purity diazoalkane solutions. As illustrated by the homologation products shown in Chart 2,

Chart 2. Representative Diazoalkane–Carbonyl Homologation Products



the catalytic carbon insertion methods we have reported tolerate severe steric crowding in the diazoalkane, giving congested quaternary carbon atoms in excellent yield (96% of **15**).[11] Noteworthy is that disubstituted (internal) diazo compounds react smoothly with unstrained electrophiles, and the procedures are scalable. An excellent demonstration of preparative utility is given by the synthesis of **16** in 97% yield from 1 g (5 mmol) of cyclohexanone.[11] This and other spirocycles cannot be easily prepared by enolate (or metalloenamine) alkylation or even α-vinylation protocols.[44] The 74% recovery of benzaldehyde homologation product **17** shows compatibility with common halogen groups as well as complexity in the nucleophile.[12] Finally, severe steric bulk is also tolerated in the electrophile; reaction of pivaldehyde with a citral-based diazoalkane gives neither stereomutation of the starting olefin nor isomerization into conjugation with the carbonyl group (→**18**, 88% yield).[12]

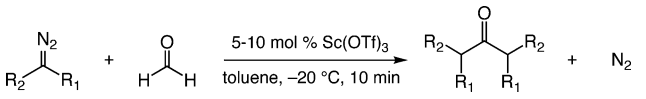
Armed with confidence that the high reaction efficiencies would translate well to the desired two-directional carbofunctionalization of formaldehyde, we turned our attention to the synthesis of 1,3-diarylacetones as a proof of concept. Their Knoevenagel condensations with diarylethanediones **e** give first tetraarylcyclopentadienones **f** and then hexarylbenzenes **g** (following Diels–Alder cycloaddition[45] with diarylethynes and expulsion of CO; see eq 1). The latter materials are now of great theoretical and practical importance in nanoscience.[46]

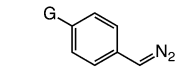
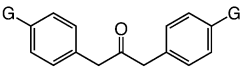
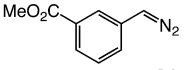
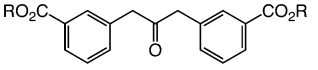
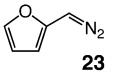
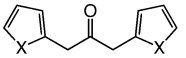
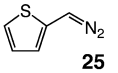
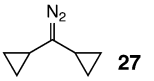
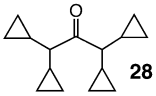
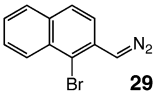
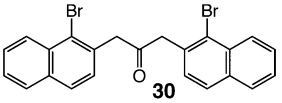
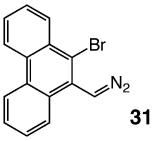
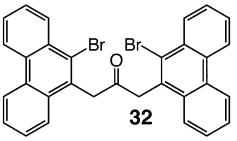


Hughes has communicated nice advances in dibenzyl ketone synthesis,[47,48] but stoichiometric amounts of either the Collman ($Na_2Fe(CO)_4$) or van Leusen (tosyl methylisocyanide) reagent are needed, and ketone yields are only moderate for electron-poor benzylic bromides. We were motivated to improve the shortcomings of existing methods in order to facilitate studies aimed at a controlled synthesis of carbon nanotube end-caps.[49−51]

Opening experiments with *p*-butylphenyldiazomethane (**19a**) identified a preferred means for delivering monomeric formaldehyde to a mixture of the catalyst and nucleophile. Attempts to use a titrated solution of formaldehyde[52,53] or to depolymerize trioxane with the Sc(OTf)$_3$ catalyst in situ[54] were thwarted by repolymerization and lower yields, respectively. However, as shown in entry 1 of Table 2, **20a** is isolated in 88% yield by "cracking" paraformaldehyde with a heat gun and

Table 2. Symmetric Ketones by Catalytic Chain Elongation with CH_2O[a]



entry	diazoalkane	yield (%)[b]	product	yield (%)[c]
1	 **19a** G = *n*-Bu	82	 **20a** G = n-Bu	88
2	**b** G = OMe	78	**b** G = OMe	83
3	**c** G = NO_2	94	**c** G = NO_2	84
4	**d** G = CN	82	**d** G = CN	86
5	**e** G = C≡CTMS	84	**e** G = C≡CH	81
6	 **21**	51	 **22a** R = Me **b** R = H	90
7	 **23**	37		74
8	 **25**	45	**24** X = O **26** X = S	76
9[d]	 **27**	28	 **28**	55
10	 **29**	85	 **30**	74
11	 **31**	81	 **32**	67[e]

[a]For the conditions above with flash pyrolysis $(CH_2O)_n{\cdot}H_2O$. [b]Over three steps based on ^{19}F NMR titration with *o*-$FC_6H_5CO_2H$. [c]Isolated yield after column chromatography. [d]Run with Sc(tmhd)$_3$. [e]See text.

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passing the gas through a warm steel cannula[55] into a toluene suspension of dry $Sc(OTf)_3$ with simultaneous addition of **19a** at −20 °C. Reactions are complete in less than 10 min, and efficiency stays high with representative electron-donating (**20b**, entry 2) and -withdrawing groups (**20c,d**, entries 3 and 4). The product of entry 5 (**20e**) is noteworthy because the alkyne substituents are suitable handles for accessing larger phenylene oligomers and dendrimers.[46] As shown in entry 6 of Table 2, ester groups are also tolerated. LiOH hydrolysis of **22a** gives **22b**, a diacid natural product found in the bark of *Cerbera manghas* that may exert a role in the plant's analgesic, anticonvulsant, cardiotonic, and hypotensive properties.[24] Hetereoaromatic (**23** and **25**, entries 7 and 8) and aliphatic nucleophiles (**27**) are also viable. The product of entry 9 is a novel tetrasubstituted acetone which exhibits a preference for $Sc(tmhd)_3$ (tmhd = 2,2,6,6-tetramethyl-3,5-heptanedianato, or *t*-butyl(acac)) as the catalyst, consistent with other reactions involving dialkyl diazomethanes.[11] The lower 55% yield recorded for **28** is still respectable given the double β-branching present in diazoalkyl component **27**.

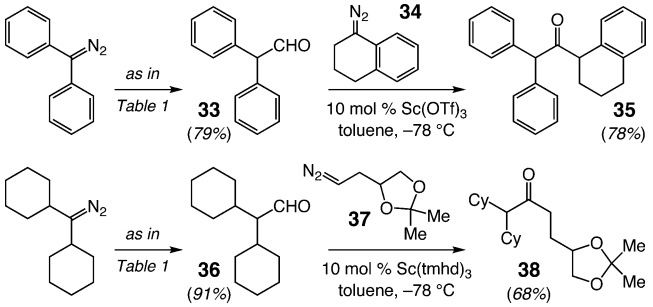
Lastly, the bis(arylated) propan-2-ones **30** and **32** are now structures available to our colleagues for the elaboration of bowl-shaped polyarenes and carbon nanotube end-caps.[56,57] Previous methodologies[48] produce these ketones only with difficulty or not at all, but the double homologation reactions (entries 10 and 11) proceed in workable yield and add insight concerning steric hindrance in the diazoalkane. The yield of product from bromonaphthyldiazomethane **29** is 74%, just 10% lower than that for 2-bromophenyldiazomethane (data not shown). However, with bromophenanthryldiazomethane **31**, the predominant product (85% yield) is the arylacetaldehyde. Presumably, the greater steric bulk in the reactant diminishes the rate of the second formal C−H insertion. The reported 67% yield for **32** is based on two steps in which the arylacetaldehyde has been resubjected to the reaction conditions (without formaldehyde) after filtration through a pad of silica.

The predominance of a monoinsertion product observed with a doubly *o*-substituted reagent like **31** (entry 11) derives from the fact that thermal cracking of paraformaldehyde invariably introduces an excess of monomeric electrophile as the reaction takes place. This further suggests that successful bidirectional syntheses with the less hindered nucleophiles (entries 1−10) may benefit from low solubility of the gaseous formaldehyde under the reaction conditions (toluene, −20 °C). In any event, we now find that other bulky diazoalkanes show a similar reluctance toward bidirectional product formation, and this permits a straightforward entry to nonsymmetrical ketones. For instance, as shown in Scheme 4, diphenyl and dicyclohexyl diazomethane give rise to the corresponding disubstituted acetaldehydes **33** and **36** in 79 and 91% yield under the former conditions of Table 2. Succeeding mergers with two different diazo compounds (**34** and **37**) then provide dissymmetric alkanones **35** and **38** in good yield. Additional experimentation will be needed to establish the full scope of α-substituted aldehyde and acyclic ketone synthesis based on tandem formaldehyde homologation, but such opening results certainly underscore the advantages of its implicit modularity.

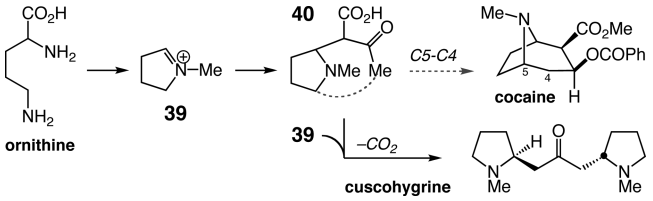
As a demonstration of utility for the double homologation method, we targeted a pair of bis(pyrrolidine) alkaloids found in the leaves of *Erythroxylon coca*. Structure elucidation[58,59] of C_2-symmetric cuscohygrine (Scheme 5) was first reported in 1889, long before its reduction product (−)-dihydrocuscohygrine (see **44**, Scheme 6) was identified in the same plant and in members of the Erythroxylaceae family.[60−62] Labeling studies confirm that the metabolites are byproducts of tropane alkaloid biosynthesis, and they often coextract with other Solanaceae alkaloids.[63] Specifically, ornithine gives rise to *N*-methyl-Δ^1-pyrrolinium **39**, affording hygrine-1-carboxylic acid (**40**) upon its reaction with acetoacetic acid.[63] Whereas dehydrogenation and internal C−C bond formation afford the tropane skeleton, decarboxylation of **40** and condensation with a second equivalent of **39** gives cuscohygrine. Along with bioactivity studies,[64,65] two total syntheses[66,67] of dihydrocuscohygrine have appeared in which absolute configuration is secured by the use of a chiral auxiliary or enzyme catalysis.

A more concise path of synthesis for the natural products features two-directional formaldehyde homologation and is shown in Scheme 6. We had planned to begin the sequence with commercially available *N*-methyl prolinol, as this would furnish the target molecules without the need for a protecting group. However, upon oxidation, the amino aldehyde **41b** was unstable and difficult to isolate in pure form. The more hindered *N*-benzyl aldehyde **41a** proved to be more robust and was easily prepared from (*S*)-proline on gram scale by the

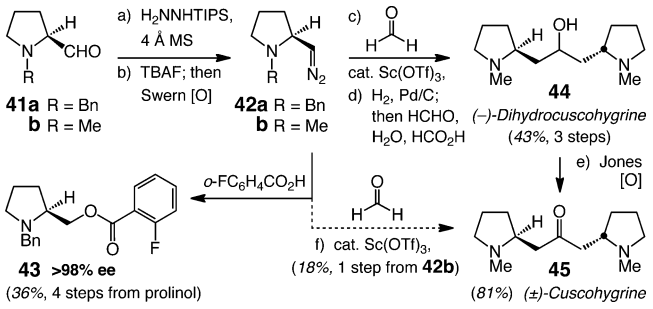
Scheme 4. Rates for the Tandem C−H Insertion Process Decrease with Bulky Diazo Compounds, Permitting Access to Dissymmetric Ketones



Scheme 5. Bis(pyrrolidine) Alkaloids Result from a Divergence in the Biosynthetic Pathway That Gives Tropane Alkaloids Such as Cocaine



Scheme 6. Short Enantiospecific Synthesis of *Erythroxylon* Alkaloids by Two-Stage Carbon Insertion with a Chiral Diazomethyl(pyrrolidine)



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sequence: Fisher esterification, N-benzylation, reduction, and Swern reoxidation. The needed aldehyde→diazomethyl conversion was then achieved as described above (Scheme 3) with temporary *N*-TIPS protection to prevent the formation of azine.[30,32] In two flasks over the three steps of condensation, desilylation, and Swern oxidation,[29] (diazomethyl)pyrrolidine **42a** forms in 36% yield based on the purified *o*-fluorobenzoate **43**. ^{19}F NMR analysis of the esterification reaction serves to establish a titer for the solution of diazoalkane, which is not concentrated or even warmed. Notably, chiral SFC analysis of ester **43** shows that it forms in >98% enantiomeric excess, confirming that no racemization occurs during diazotization. We thus turned our attention to the key diazoalkyl insertion step. Under our standard conditions (Table 1), a di-*N*-benzyl ketone was recovered in an unoptimized 60% yield after silica gel chromatography. However, due to growing concern that this sensitive material might racemize or epimerize upon exposure to mild acid (vide infra), the homologation product (>98% ee by SFC analysis) was taken on without purification. We were delighted to find that debenzylation and subsequent methylation[68] in the same pot gives (−)-dihydrocuscohygrine (**44**) in 43% yield from **42a**. The seven resonances visible in its ^{13}C NMR spectrum are a signature of the C_2-symmetry and indicate that **44** was prepared free of a *meso* contaminant. In addition, the target was formed in 98% ee on the basis of chiral GC analysis ($[\alpha]_D^{23}$ = −102, *c* 0.76, acetone; lit.[34] $[\alpha]_D^{23}$ = −105, *c* 2.05 acetone).

Success in this route can be attributed to a fortuitous reduction of the central carbonyl group under the conditions of hydrogenolysis. In this manner, (−)-dihydrocuscohygrine is prepared without the intermediacy of cuscohygrine, which is yet to be obtained in optically active form.[60,66] This results from facile stereomutation, presumably by a retro-Mannich or retro-Michael (*β*-elimination) pathway.[69] The existence of related isomerizations within the oxindole family of alkaloids for structures like horsfiline,[70] which lack an *α*-hydrogen atom, would appear to point to the former as the operative mechanism. By analogy to studies by Stapper and Blechert, we failed to find conditions for mild, efficient oxidation of **44** to cuscohygrine (**45**).[66] Jones oxidation affords the ketone in 81% yield as a racemate (step e, Scheme 6), but other reagents give incomplete conversion or decomposition of the material. Despite the instability of amine carboxaldehyde **41b**, its corresponding diazo compound **42b** could be prepared in 23% yield over four steps by careful handling of the aldehyde. In a final attempt to access homochiral cuscohygrine, **42b** was treated with formaldehyde and Sc(OTf)$_3$, and the mixture was filtered through neutral alumina. The natural product is formed cleanly in low yield, but ^{1}H NMR analysis still shows it to be indistinguishable from both synthetic and naturally occurring cuscohygrine, again implying that the *meso* and D,L forms are interconverting even under neutral conditions.[60,66]

CONCLUSIONS

In conclusion, we report an efficient catalytic approach to ketones by a two-stage coupling event between monomeric formaldehyde and non-carbonyl-stabilized diazo compounds. The reaction is quite suitable for preparing 1,3-diarylacetone building blocks for materials science, and well-established methods for the synthesis and handling of diazoalkane stock solutions are provided herein. The mild reaction conditions, together with the brevity ensured by a bidirectional strategy, have facilitated an enantiospecific synthesis of the bis(pyrrolidine) alkaloid (−)-dihydrocuscohygrine starting from (*S*)-*N*-benzyl prolinol. Noteworthy is that sensitive, *α*-chiral aldehydes are transformed to the corresponding diazo compounds for use in esterification or homologation reactions with no racemization.

EXPERIMENTAL SECTION

General. Any synthetic chemist who wishes to repeat or adapt experiments reported herein should exercise caution and recognize that all diazoalkanes are likely toxic and shock-sensitive. Although these materials can be assayed in neat form by both NMR and IR spectroscopy, our procedures do not call for isolation, distillation, or even warming of the potentially hazardous diazo compounds. All transfers and manipulations, including reagent storage, are carried out in solution at low temperature, and the active titer for a given diazo compound is conveniently obtained by acidic quench of a stock solution aliquot with 2-fluorobenzoic or benzoic acid. In cases where a volatile diazoalkane is being prepared or a large-scale (>1 g) experiment is desirable, adequate precautions should be taken, such as the use of a safety shield. Gloves must be worn at all times when handling diazoalkane solutions and vessels.

IR spectra were recorded on a FT-IR spectrophotometer, ν_{max} in cm^{-1}. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer with chemical shifts reported in parts per million from TMS with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26). ^{13}C NMR spectra were recorded on the same instrument (100 MHz) with complete proton decoupling. Chemical shifts are reported in parts per million from TMS with solvent as the internal standard ($CDCl_3$: δ 77.23). High-resolution mass spectra were obtained with a TOF detector using Data Acquisition in Real Time (DART) or with ESI-TOF in positive ion mode. The enantiomer ratio for **43** was determined by supercritical fluid chromatography (SFC) with a Chiralcel OD-H column (0.46 cm ϕ × 25 cm). Enantiopurity for **44** was determined by chiral GLC analysis on a Chiraldex BDM column (30 m × 0.25 mm) with the injection inlet, column, and detector all set to a constant temperature of 250 °C.

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an atmosphere of nitrogen in dry, degassed solvents using standard Schlenk or vacuum-line techniques. THF, Et_2O, toluene, CH_2Cl_2, DMF, pentane, and hexanes were dispensed from a multiport, inert solvent purification system under a positive pressure stream of high-purity argon. Triisopropylsilylhydrazine was prepared as formerly described.[33] 4-Butylbenzaldehyde and 1,1,3,3-tetramethylguanidine were vacuum distilled over calcium hydride. 4-Methoxybenzaldehyde, 4-formylbenzonitrile, 4-((trimethylsilyl)ethynyl)benzaldehyde, methyl 3-formylbenzoate, furfural, thiophene-2-carboxaldehyde, dicyclopropylmethanone, dicyclohexylmethanone, and 3,4-dihydronaphthalen-1(2*H*)-one were vacuum distilled. 4-Nitrobenzaldehyde was recrystallized from water−isopropyl alcohol. $Pb(OAc)_4$, after dissolution in minimal hot glacial acetic acid, deposited as bright white needles upon cooling. The crystals were washed in a fritted Schlenk filter with dry pentane, dried under high vacuum, and then stored in a glovebox at −20 °C. Sc(OTf)$_3$ (99%) was finely powdered and dried at 200 °C over P_2O_5 for 24 h under vacuum (approximately 0.1 mm of Hg). 2-Fluorobenzoic acid was sublimed at 100 °C under vacuum and dried over P_2O_5. Hydrazine hydrate, TBAF, 2-(2,2-dimethyl-1,3-dioxolan-4-yl)-acetaldehyde, 9-bromophenanthrene, 1-bromo-2-methylnaphthalene, benzophenone, powdered 4 Å molecular sieves, (*S*)-1-methyl-2-pyrrolidinemethanol, benzoic acid, and Sc(tmhd)$_3$ were obtained commercially and used as received. The procedure below for preparing an unprotected arylhydrazone is based on one reported previously.[71] Flash column chromatography was carried out with silica gel 60 and driven with compressed air. Analytical TLC was performed with 250 μm silica gel 60 F_{254} plates and either a ceric ammonium molybdate, potassium permanganate, ninhydrin, or dinitrophenylhydrazine stain for spot visualization.

Representative Procedure for Synthesis and Handling of Aliphatic Diazoalkanes (Benzoic Acid Quench). *(S)-(−)-Citronellal N-(Triisopropylsilyl)hydrazone (1).* A 50 mL round-bottom flask equipped with a Teflon-coated stir bar and a jointed vacuum

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adapter was charged with powdered 4 Å molecular sieves (4 g) and then flame-dried under high vacuum. After backfilling with nitrogen, the vacuum adapter was swapped for a rubber septum, and (*S*)-(−)-citronellal (1.70 g, 11.0 mmol, 1.0 equiv) and THF (22 mL) were added successively with stirring. The suspension was cooled to 0 °C, and triisopropylsilylhydrazine (2.08 g, 11.0 mmol, measured by mass difference into a gastight syringe) was slowly added dropwise over 2 h with a syringe pump. After 30 min of additional stirring, the mixture was filtered through a pad of Celite in a sintered glass Schlenk filter into a dry 100 mL round-bottom flask cooled to 0 °C. The original flask, molecular sieves, and Celite were washed with two additional 10 mL portions of cold Et_2O. The resulting homogeneous filtrate was concentrated on a rotovap equipped with an oil-free diaphragm pump (3−10 Torr), affording 3.57 g (11.0 mmol, >98%) of **1** as a colorless oil (~9:1 *E*:*Z* mixture, >98% pure by ^{1}H NMR analysis). If not used directly in a subsequent oxidation reaction, this material was stored under nitrogen at −20 °C.

*(S)-3,7-Dimethyl-1-diazooct-6-ene (**2**).* A flame-dried 50 mL round-bottom flask with an oversized Teflon-coated stir bar was charged with **1** (490 mg, 1.5 mmol, 1.0 equiv) and 10 mL of THF. After cooling the colorless solution to 0 °C, 1.51 mL of TBAF (1.0 M in THF, 1.51 mmol, 1.0 equiv) was added by syringe, at which time a yellow-orange discoloration was observed. The solution was stirred for 10 min and then concentrated with a nitrogen purge. Without purification and in the same vessel, the crude hydrazone was freed of residual solvent under vacuum, purged with nitrogen, and redissolved in 15 mL of DMF and 3 mL of 1,1,3,3-tetramethylguanidine (36.0 mmol, 24 equiv). The resulting yellow solution was cooled to −45 °C (dry ice/acetonitrile bath) and $Pb(OAc)_4$, finely powdered and weighed into a large vial in a glovebox (736 mg, 1.66 mmol, 1.1 equiv), was added in a single portion. After 45 min of stirring at −45 °C, 15 mL of precooled pentane was added and the mixture was stirred very vigorously for 1 min. The upper, bright yellow pentane layer was removed by syringe and transferred to a 100 mL pear-shaped flask and cooled to −78 °C. Extraction was repeated two to three more times (15 mL of pentane) until the extract was no longer visibly colored. The organic layers were washed twice with 15 mL of saturated ammonium chloride and once with 15 mL of 30% aqueous potassium hydroxide.[31] In each case, prolonged (>30 s) vigorous stirring was allowed, the aqueous layer was removed by syringe, and warming above the freezing point (−20 °C) was required for miscibility; these washes serve (respectively) to remove residual tetramethylguanidine and DMF from the organic extract—a prerequisite for efficient catalytic carbon insertion but not simple esterification.

*(S)-3,7-Dimethyloct-6-en-1-yl Benzoate (**3**).* The solution of diazoalkane **2** was transferred with rinsing (freezing the final aqueous wash is most convenient) to a 100 mL round-bottom flask and concentrated under high vacuum at −45 °C to give **2** as a yellow oil. The NMR data that follow represent direct assay of this material without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (t, J = 6.4 Hz, 1H), 2.32−2.23 (m, 2H), 1.92−1.83 (m, 2H), 1.59 (s, 3H), 1.51 (s, 2H), 1.46−1.07 (m, 4H), 0.89 (d, J = 6.8 Hz, 3H). Typically, the diazoalkane is kept cold, immediately redissolved in toluene, and transferred (quantitatively, with rinsing) by cannula to a 1.00 mL volumetric flask. The active titer can be determined by esterification with benzoic acid. Thus, 100 μL of the stock solution was diluted with 1 mL of THF in a 5 mL round-bottom flask, cooled to −45 °C, and treated with benzoic acid dropwise by syringe (166 μL of a 1.0 M solution in THF, 0.166 mmol, 1.1 equiv based on theoretical). Upon slow warming from −45 °C, the reaction mixture became colorless and nitrogen evolution was observed. The mixture was diluted with Et_2O (25 mL) and saturated sodium bicarbonate (25 mL) and transferred to a separatory funnel. The aqueous layer was washed with two additional 10 mL volumes of Et_2O. The combined organic layers were dried over magnesium sulfate and concentrated to a light yellow oil. Purification by silica gel chromatography (TLC R_f = 0.28 in 25:1 hexanes/ethyl acetate) afforded 23.6 mg of benzoate ester **3** (60% yield, indicative of a 0.91 M stock solution of diazoalkane **2**). IR (thin film): 2860 (w), 2913 (w), 1719 (s), 1451 (w), 1379 (w), 1314 (w), 1270 (s), 1175 (w), 1110 (m), 1070 (w), 1026 (w), 709 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, J = 8.4, 1.3 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.44 (m, 2H), 5.10 (t, J = 6.6 Hz, 1H), 4.36 (m, 2H), 2.01 (m, 2H), 1.86−1.21 (m, 5H), 1.67 (s, 3H), 1.60 (s, 3H), 0.97 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 132.9, 129.6, 128.4, 124.7, 117.1, 63.6, 37.2, 35.7, 35.6, 29.7, 25.9, 25.6, 19.7, 17.8. HRMS (ESI+) calcd for $C_{17}H_{25}O_2^+$ $[M + H]^+$: 261.1855; found 261.1856.

1-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylidene)-2-(triisopropylsilyl)hydrazone. 2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetaldehyde (0.166 g, 1.15 mmol), THF (2.5 mL), and triisopropylsilylhydrazine (0.216 g, 1.15 mmol, 1.0 equiv) were combined with powdered 4 Å molecular sieves exactly as described above for structure **1**. Filtration and concentration provided 0.362 g (1.15 mmol, >98%) of product as a colorless oil (~3:2 *E*:*Z* mixture, >98% pure by ^{1}H NMR analysis).

Alternative Procedure for Diazoalkane Synthesis and Manipulation (2-Fluorobenzoic Acid Quench). *4-(2-Diazoethyl)-2,2-dimethyl-1,3-dioxolane.* A 50 mL round-bottom flask equipped with a large Teflon-coated stir bar was charged with 1-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylidene)-2-(triisopropylsilyl)-hydrazone (362 mg, 1.15 mmol) and 10 mL of THF. After cooling the colorless solution to 0 °C, 1.15 mL of TBAF (1.0 M in THF, 1.15 mmol, 1.0 equiv) was added by syringe, at which point a bright orange discoloration immediately occurred. The solution was stirred for 10 min and then concentrated under low vacuum on a rotovap. Without purification and in the same flask, the crude hydrazone was freed of residual solvent under high vacuum, backfilled with nitrogen, and redissolved in 7.6 mL of DMF and 2.88 mL of 1,1,3,3-tetramethylguanidine (23.0 mmol, 20 equiv). The resulting light pink solution was cooled to −45 °C (dry ice/1:1 ethanol−ethylene glycol),[72] and $Pb(OAc)_4$, finely powdered and weighed into a vial in a glovebox (561 mg, 1.26 mmol, 1.1 equiv), was added in a single portion. After 45 min of stirring at −45 °C, 50 mL of ice cold pentane was added and the mixture was transferred to a separatory funnel. Upon removing the colored organic layer, the DMF layer was washed three times with 25 mL of cold pentane and discarded as waste. The combined extracts were quickly washed twice with cold 25 mL volumes of saturated ammonium chloride and once with 25 mL of cold (−20 °C) 30% aqueous potassium hydroxide.[31] The diazoalkane solution was then dried over potassium carbonate, filtered with a sintered glass fritted filter, and concentrated under high vacuum at −45 °C to afford 4-(2-diazoethyl)-2,2-dimethyl-1,3-dioxolane as an orange oil. The oil was immediately dissolved in toluene and transferred (quantitatively, with rinsing) by cannula to a 1.00 mL volumetric flask. The active titer was assayed by esterification with 2-fluorobenzoic acid.[41] Thus, 100 μL of the stock solution was added dropwise by syringe to a cold (−45 °C) flask containing a 1.0 M Et_2O solution of 2-fluorobenzoic acid (16 mg, 0.115 mmol, 1.0 equiv based on theoretical). Upon warming from −45 °C, the reaction mixture became colorless and nitrogen evolution was observed. The solvent was removed under reduced pressure, and the contents of the flask were dissolved in $CDCl_3$ for ^{19}F NMR analysis. Based on integration of the unreacted 2-fluorobenzoic acid to the newly formed benzoate ester (1.44:1), the active titer for the diazoalkane stock solution in toluene was obtained (0.47 M, 41% yield).

Representative Procedure for the Preparation of an Unprotected Arylhydrazone. *4-Nitrobenzaldehyde Hydrazone.* In a 2 dram glass vial containing a Teflon-coated stir bar, 4-nitrobenzaldehyde (0.453 g, 3.00 mmol) was suspended in 2.0 mL of hydrazine hydrate. After sealing the vial with a Teflon-lined screw cap, the heterogeneous mixture was stirred rapidly with heating at 100 °C. After 6 h, the mixture was cooled to 23 °C and the product was extracted with three 2 mL volumes of CH_2Cl_2. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 0.479 g (2.90 mmol, 96%) of an oil. The material was >98% pure by ^{1}H NMR spectroscopy and proved to be a >98:2 *E*:*Z* mixture.

*2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethyl 2-Fluorobenzoate (**4**).* 4-(2-Diazoethyl)-2,2-dimethyl-1,3-dioxolane was prepared in 41% yield as a 0.47 M solution in toluene from 0.362 g (1.15 mmol) of (*E*)-1-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylidene)-2-(triisopropylsilyl)hydrazine based on esterification to give 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl 2-fluorobenzoate (**4**). Purification by flash

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chromatography (TLC R_f = 0.35 in 97.5:2.5 hexanes/ethyl acetate) delivered the ester as a colorless oil. IR (thin film): 2400 (w), 1717 (s), 1613 (w), 1457 (w), 1372 (w), 1159 (m), 1034 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dt, J = 7.4, 1.9 Hz, 1H), 7.55−7.47 (m, 1H), 7.19 (dt, J = 7.8, 1.1 Hz, 1H), 7.15−7.09 (m, 1H), 4.54−4.23 (m, 3H), 4.10 (dd, J = 8.1, 6.0 Hz, 1H), 3.63 (dd, J = 8.1, 7.0 Hz, 1H), 2.11−1.94 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (d, J = 2.9 Hz), 162.1 (d, J = 206.8 Hz), 134.7 (d, J = 7.3 Hz), 132.3, 124.1 (d, J = 3.0 Hz), 118.8 (d, J = 7.9 Hz), 117.2 (d, J = 14.0 Hz), 109.1, 73.4 (d, J = 2.0 Hz), 69.5 (d, J = 3.9 Hz), 62.4, 32.9, 27.1, 25.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ 109.8. HRMS (ESI+) calcd for $C_{14}H_{18}FO_4^+$ $[M + H]^+$: 269.1189; found 269.1198.

*(Z)-Oct-5-en-1-yl Benzoate (**5**).* (*Z*)-8-Diazooct-3-ene was prepared in 42% yield as a 0.48 M solution in toluene from 0.62 g (2.09 mmol) of (*E*)-1-((*Z*)-oct-5-en-1-ylidene)-2-(triisopropylsilyl)hydrazine based on esterification to afford (*Z*)-oct-5-en-1-yl benzoate (**5**). Purification by silica gel chromatography (TLC R_f = 0.4 in 97.5:2.5 hexanes/ethyl acetate) gave the ester as a colorless oil. IR (thin film): 2779 (w), 1714 (s), 1558 (w), 1502 (w), 1488 (w), 1182 (w), 1157 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−8.03 (m, 2H), 7.59−7.53 (m, 1H) 7.47−7.41 (m, 2H), 5.42−5.28 (m, 2H), 4.32 (t, J = 6.7 Hz, 2H), 2.09−1.99 (m, 4H), 1.82−1.73 (m, 2H), 1.47−1.42 (m, 4H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 133.0, 132.1, 130.7, 129.7, 129.0, 128.5, 65.3, 29.6, 28.8, 27.2, 25.9, 20.7, 14.6. HRMS (ESI+) calcd for $C_{15}H_{21}O_2^+$ $[M + H]^+$: 233.1542; found 233.1535.

*1-Methylpiperidin-4-yl 2-Fluorobenzoate (**6**).* 4-Diazo-1-methylpiperidine was made in 37% yield as a 0.61 M solution in toluene from 0.25 g (0.88 mmol) of 1-methyl-4-(2-(triisopropylsilyl)hydrazono)-piperidine based on reaction to give 1-methylpiperidin-4-yl 2-fluorobenzoate (**6**). Purification by chromatography (TLC R_f = 0.30 in 90:10 hexanes/ethyl acetate) gave ester **6** as an oil. IR (thin film): 2388 (w), 1717 (s), 1613 (w), 1585 (w), 1520 (w), 1475 (m), 1301 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dt, J = 1.9, 7.5 Hz, 1H), 7.56−7.48 (m, 1H), 7.20 (dt, J = 1.1, 7.6 Hz, 1H), 7.13 (ddd, J = 1.1, 8.3, 10.9 Hz, 1H), 4.39−4.35 (m, 3H), 3.63−3.58 (m, 3H), 2.02−1.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (d, J = 2.9 Hz), 162.1 (d, J = 206.7 Hz), 134.7 (d, J = 7.2 Hz), 132.3 (d, J = 0.7 Hz), 124.2 (d, J = 3.0 Hz), 118.9 (d, J = 7.2 Hz), 117.2 (d, J = 17.8 Hz), 64.7, 44.7, 29.4, 26.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ 111.6. HRMS (ESI+) calcd for $C_{13}H_{20}FN_2O_2^+$ $[M + NH_4]^+$: 255.1509; found 255.1529.

*1-Cyclopropylethyl Benzoate (**7**).* (1-Diazoethyl)cyclopropane was made in 44% yield as a 1.12 M solution in toluene from 1.06 g (10.8 mmol) of (*E*)-(1-cyclopropylethylidene)hydrazine based on esterification to afford 1-cyclopropylethyl benzoate (**7**). Purification by silica gel chromatography (TLC R_f = 0.35 in 97.5:2.5 hexanes/ethyl acetate) provided the ester as a colorless oil. IR (thin film): 2321 (w), 1707 (s), 1601 (w), 1469 (w), 1451 (w), 1378 (m), 1338 (w), 1276 (m), 1216 (w), 1070 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.3 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 4.60 (qd, J = 6.3, 2.1 Hz, 1H), 1.43 (d, J = 6.3 Hz, 3H), 1.16−1.11 (m, 1H), 0.62−0.46 (m, 3H), 0.35−0.30 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 132.8, 131.1, 129.7, 128.4, 75.9, 20.1, 16.6, 3.8. HRMS (ESI+) calcd for $C_{12}H_{15}O_2^+$ $[M + H]^+$: 191.1072; found 191.1067.

*(E)-Hex-2-en-1-yl Benzoate (**8**).* (*E*)-1-Diazohex-2-ene was prepared in 52% yield as a 0.44 M solution in toluene from 0.173 g (0.644 mmol) of (*E*)-1-((*E*)-hex-2-en-1-ylidene)-2-(triisopropylsilyl)-hydrazine based on reaction to give (*E*)-hex-2-en-1-yl benzoate (**8**). Purification by flash chromatography (TLC R_f = 0.4 in 95:5 hexanes/ethyl acetate) gave the ester as a colorless oil. IR (thin film): 2433 (w), 1714 (s), 1521 (w), 1424 (w), 1315 (w), 1114 (m), 1070 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08−8.05 (m, 2H), 7.57−7.53 (m, 1H), 7.46−7.42 (m, 2H), 5.90−5.83 (m, 1H), 5.72−5.66 (m, 1H), 4.76 (dd, J = 6.4, 0.9 Hz, 2H), 2.09−2.04 (m, 2H), 1.46 (qt, J = 7.4, 7.4 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 136.6, 133.0, 130.6, 129.8, 128.5, 124.1, 66.0, 34.6, 22.3, 13.9. HRMS (ESI+) calcd for $C_{13}H_{20}NO_2^+$ $[M + NH_4]^+$: 222.1494; found 222.1496.

*Cinnamyl Benzoate (**9**).* (*E*)-(3-Diazoprop-1-en-1-yl)benzene was prepared in 59% yield as a 0.80 M solution in toluene from 0.351 g (1.16 mmol) of (*E*)-1-((*E*)-3-phenylallylidene)-2-(triisopropylsilyl)hydrazine based on reaction to give cinnamyl benzoate (**9**). Purification by silica gel chromatography (TLC R_f = 0.35 in 95:5 hexanes/ethyl acetate) gave the ester as a colorless oil. IR (thin film): 3019 (w), 2399 (w), 1717 (s), 1496 (w), 1476 (w), 1377 (w), 1118 (m), 1097 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11−8.08 (m, 2H), 7.60−7.54 (m, 1H), 7.48−7.41 (m, 4H), 7.37−7.24 (m, 3H), 6.75 (d, J = 15.9 Hz, 1H), 6.41 ppm (dt, J = 15.9, 6.4 Hz, 1H), 4.99 (dd, J = 6.4, 1.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 145.8, 136.3, 134.4, 133.1, 129.8, 128.7, 128.5, 128.2, 126.8, 123.4, 65.7. HRMS (ESI+) calcd for $C_{16}H_{18}NO_2^+$ $[M + NH_4]^+$: 256.1338; found 256.1325.

*Cyclohex-2-en-1-yl Benzoate (**10**).* 3-Diazocyclohex-1-ene was prepared in 66% yield as a 0.62 M solution in toluene from 0.402 g (1.51 mmol) of (*E*)-1-(cyclohex-2-en-1-ylidene)-2-(triisopropylsilyl)-hydrazine based on reaction to give cyclohex-2-en-1-yl benzoate (**10**). Purification by silica gel chromatography (TLC R_f = 0.4 in 95:5 hexanes/ethyl acetate) gave the ester as a clear oil. IR (thin film): 2869 (w), 1709 (s), 1602 (w), 1521 (w), 1428 (w), 1274 (m), 1177 (w), 1116 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−8.06 (m, 2H), 7.55−7.51 (m, 1H), 7.44−7.40 (m, 2H), 6.01−5.99 (m, 1H), 5.87−5.83 (m, 1H), 5.54−5.51 (m, 1H), 2.15−2.11 (m, 1H), 2.07−1.93 (m, 2H), 1.90−1.81 (m, 2H), 1.71−1.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 132.8, 132.8, 130.8, 129.6, 128.3, 125.7, 68.6, 28.4, 25.0, 19.0. HRMS (ESI+) calcd for $C_{13}H_{15}O_2^+$ $[M + H]^+$: 203.1072; found 203.1101.

*1-Phenylpropyl Benzoate (**11**).* (1-Diazopropyl)benzene was prepared in 88% yield as a 1.33 M solution in toluene from 0.351 g (2.37 mmol) of (*E*)-(1-phenyl-propylidene)hydrazine based on esterification to give 1-phenylpropyl benzoate (**11**). Purification by flash chromatography (TLC R_f = 0.35 in 95:5 hexanes/ethyl acetate) afforded the ester as a colorless oil. IR (thin film): 2433 (w), 1714 (s), 1601 (w), 1520 (w), 1451 (w), 1423 (m), 1274 (w), 1177 (w), 1081 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12−8.08 (m, 2H), 7.59−7.53 (m, 1H), 7.45−7.28 (m, 7H), 5.93 (t, J = 6.4 Hz, 1H), 2.17−1.86 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 140.9, 133.2, 130.8, 129.9, 128.7, 128.6, 128.1, 126.7, 78.2, 29.8, 10.2. HRMS (ESI+) calcd for $C_{16}H_{20}NO_2^+$ $[M + NH_4]^+$: 258.1494; found 258.1470.

*1-(o-Tolyl)ethyl Benzoate (**12**).* 1-(1-Diazoethyl)-2-methylbenzene was made in 82% yield as a 1.45 M solution in toluene from 1.60 g (10.8 mmol) of (*E*)-(1-(*o*-tolyl)ethylidene)hydrazine based on reaction to afford 1-(*o*-tolyl)ethyl benzoate (**12**). Purification by silica gel chromatography (TLC R_f = 0.35 in 95:5 hexanes/ethyl acetate) gave the ester as a colorless oil. IR (thin film): 2979 (w), 2897 (w), 1712 (s), 1584 (w), 1476 (w), 1391 (w), 1276 (m), 1174 (w), 1114 (w), 1069 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12−8.09 (m, 2H), 7.60−7.51 (m, 2H), 7.48−7.42 (m, 2H), 7.28−7.16 (m, 3H), 6.34 (q, J = 6.5 Hz, 1H), 2.46 ppm (s, 3H), 1.66 (d, J = 6.5 ppm, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 140.3, 134.9, 133.0, 130.60, 130.59, 129.7, 128.5, 127.8, 126.5, 125.4, 70.1, 21.7, 19.3. HRMS (ESI+) calcd for $C_{16}H_{17}O_2^+$ $[M + H]^+$: 241.1229; found 241.1212.

*1,2,3,4-Tetrahydronaphthalen-1-yl Benzoate (**13**).* 1-Diazo-1,2,3,4-tetrahydronaphthalene was prepared in 80% yield as a 1.40 M solution in toluene from 0.54 g (3.37 mmol) of (*E*)-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazine based on reaction to give 1,2,3,4-tetrahydronaphthalen-1-yl benzoate (**13**). Purification by flash chromatography (TLC R_f = 0.40 in 95:5 hexanes/ethyl acetate) gave the ester as a colorless oil. IR (thin film): 2253 (w), 1709 (s), 1584 (w), 1350 (w), 1269 (w), 1211 (m), 1155 (w), 1070 (w), 1026 (w), 1002 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, J = 8.4, 1.3 Hz, 2H), 7.57 (dt, J = 7.4, 1.3 Hz, 1H), 7.47−7.41 (m, 3H), 7.31−7.27 (m, 1H), 7.24−7.20 (m, 2H) 6.32 (t, J = 4.4 Hz, 1H), 3.00−2.94 (m, 1H), 2.88−2.83 (m, 1H), 2.18−2.09 (m, 3H), 1.96−1.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 138.3, 134.9, 133.1, 130.9, 129.9, 129.8, 129.3, 128.5, 128.4, 126.3, 70.9, 29.5, 29.4, 19.4. HRMS (ESI+) calcd for $C_{17}H_{17}O_2^+$ $[M + H]^+$: 253.1229; found 253.1219.

*(10-Bromophenanthren-9-yl)methyl Benzoate (**14**).* 9-Bromo-10-(diazomethyl)phenanthrene was prepared in 81% yield as a 0.28 M solution in toluene from 0.122 g (0.408 mmol) of (*E*)-((10-bromophenanthren-9-yl)methylene)hydrazine based on reaction to afford (10-bromophenanthren-9-yl)methyl benzoate (**14**). Purification by flash chromatography (TLC R_f = 0.35 in 95:5 hexanes/ethyl acetate)

gave the ester as a colorless, crystalline solid; mp = 135−136 °C. IR (thin film): 2976 (m), 1716 (s), 1521 (w), 1476 (w), 1423 (w), 1271 (m), 1113 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76−8.70 (m, 2H), 8.59−8.56 (m, 1H), 8.21−8.18 (m, 1H), 8.04−8.01 (m, 2H), 7.75−7.63 (m, 4H), 7.55−7.50 (m, 1H), 7.41−7.35 (m, 2H), 6.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 133.2, 131.8, 131.4, 130.4, 130.12, 131.10, 130.05, 129.98, 129.95, 129.7, 128.5, 128.3, 127.95, 127.94, 127.3, 125.1, 123.4, 122.8, 65.4. HRMS (ESI+) calcd for $C_{22}H_{16}BrO_2^+$ $[M + H]^+$: 391.0334; found 391.0360.

*1-Butyl-4-(diazomethyl)benzene (**19a**).* Prepared as a 1.23 M solution in 82% yield from 0.574 g of (4-butylbenzylidene)hydrazone (3.00 mmol) by the known procedure.[29] Used in a reaction with formaldehyde immediately after its preparation, otherwise stored cold at −78 °C.

Representative Procedure for the Bidirectional Synthesis of Ketones. *1,3-Bis(4-butylphenyl)propan-2-one (**20a**).* In a glovebox, $Sc(OTf)_3$ (35 mg, 0.071 mmol, 0.095 equiv) was added to a 25 mL round-bottom flask containing a Teflon-coated stir bar. The flask was sealed with a rubber septum, removed from the glovebox, and taken to a fume hood. Under positive nitrogen pressure, the $Sc(OTf)_3$ was suspended in toluene (7.5 mL, 0.10 M) and the flask was cooled to −20 °C (ethylene glycol−ethanol/dry ice bath).[72] Monomeric formaldehyde was then introduced by "cracking" solid paraformaldehyde (thermal depolymerization, >150 °C) in a separate flask and allowing the gas generated to pass through a steel wide bore (16 gauge) cannula into the suspension of $Sc(OTf)_3$ in toluene. Typically, 30 equiv of the polymer was dispensed for multiple reactions so that the amount of formaldehyde consumed could be determined by mass difference (in this case ∼100 mg, 3.3 mmol, 4.4 equiv). While the formaldehyde gas was bubbling through the reaction mixture, a solution of **19a** (0.61 mL of a 1.23 M solution in toluene, 0.75 mmol, 1.0 equiv) was added dropwise over 5 min. At the end of the addition, the bubbling of formaldehyde gas was stopped and the reaction was stirred at −20 °C for 10 min. The reaction then mixture was poured into a separatory funnel, diluted with 20 mL of Et_2O, and washed with 40 mL portions of water and saturated sodium chloride. After collecting the organic layer, it was dried over sodium sulfate, filtered, and concentrated to a light yellow oil that was purified by silica gel chromatography (TLC R_f = 0.30 in 97.5:2.5 hexanes/ethyl acetate). These operations delivered 106 mg (0.33 mmol, 88% yield) of **20a** as a colorless oil. IR (thin film): 2928 (m), 2857 (m), 1702 (s), 1606 (w), 1512 (w), 1457 (w), 1276 (w), 1103 (m), 823 (w) 650 (w), 537 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.1 Hz, 4H), 7.05 (d, J = 8.0 Hz, 4H), 3.67 (s, 4H), 2.85 (t, J = 6.4 Hz, 4H), 1.59 (dt, J = 6.8, 4.6 Hz, 4H), 1.35 (dd, J = 15.0, 7.4 Hz, 4H), 0.92 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 141.9, 131.4, 129.6, 129.0, 48.9, 35.5, 33.8, 22.6, 14.2. HRMS (ESI+) calcd for $C_{23}H_{31}O^+$ $[M + H]^+$: 323.2375; found 323.2357.

*(4-Methoxyphenyl)diazomethane (**19b**).* Prepared as a 1.47 M toluene solution in 78% yield from 0.297 g of (4-methoxybenzylidene)hydrazone (1.97 mmol) by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*1,3-Bis(4-methoxyphenyl)propan-2-one (**20b**).* Prepared according to the representative procedure given above from 0.248 mmol of **19b** (0.169 mL of a 1.47 M solution in toluene, 1.0 equiv) and 10 mg of $Sc(OTf)_3$ (0.02 mmol, 0.08 equiv). Product **20b** was recovered as a colorless oil (27.8 mg, 83% yield). Characterization data for this material have been reported previously.[47]

*(4-Nitrophenyl)diazomethane (**19c**).* Prepared as a 1.51 M toluene solution in 94% yield from 0.240 g of 4-nitrobenzaldehyde hydrazone (1.58 mmol) by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*1,3-Bis(4-nitrophenyl)propan-2-one (**20c**).* Prepared according to the representative procedure given above from 1.51 mmol of **19c** (1.00 mL of a 1.51 M solution in toluene, 1.0 equiv) and 44 mg of $Sc(OTf)_3$ (0.090 mmol, 0.06 equiv). Product **20c** was recovered as a recovered as a crystalline solid (190 mg, 84% yield). Characterization data for this material have been reported previously.[73]

*4-(Diazomethyl)benzonitrile (**19d**).* Prepared as a 0.271 M toluene solution in 82% yield from 0.240 g of 4-(hydrazonomethyl)benzonitrile (1.65 mmol) by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*4,4′-(2-Oxopropane-1,3-diyl)dibenzonitrile (**20d**).* Prepared according to the representative procedure given above from 0.136 mmol of **19d** (0.502 mL of a 0.271 M solution in toluene, 1.0 equiv) and 6.6 mg of $Sc(OTf)_3$ (0.013 mmol, 0.10 equiv). Product **20d** was isolated as a white solid (15.2 mg, 86% yield). Characterization data for this material have been reported previously.[74]

*((4-(Diazomethyl)phenyl)ethynyl)trimethylsilane (**19e**).* Prepared as a 1.98 M toluene solution in 84% yield from 0.266 g of (4-((trimethylsilyl)ethynyl)benzylidene)hydrazone (1.23 mmol) by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*1,3-Bis(4-ethynylphenyl)propan-2-one (**20e**).* Prepared according to the representative procedure given above from 1.00 mmol of **19e** (0.505 mL of a 1.98 M solution in toluene, 1.0 equiv) and 50.0 mg of $Sc(OTf)_3$ (0.102 mmol, 0.10 equiv). After purification by flash chromatography (TLC R_f = 0.33 in 12:1 hexanes/ethyl acetate), which results in desilylation, 104 mg of **20e** was obtained as a white solid in 81% yield; mp = 132 °C. IR (thin film): 3293 (s), 3032 (w), 2889 (w), 1716 (s) 1508 (m), 1414 (m), 1335 (m), 1303 (m), 1108 (w), 1054 (m), 1020 (w), 847 (m), 823 (m), 641 (m), 543 (m), 515 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.42 (m, 1H), 7.12−7.08 (m, 1H), 3.72 (s, 1H), 3.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 147.1, 134.6, 132.6, 129.6, 121.2, 83.4, 49.2. HRMS (ESI+) calcd for $C_{19}H_{15}O^+$ $[M + H]^+$: 259.1123; found 259.1124.

*Methyl 3-(Diazomethyl)benzoate (**21**).* Prepared as a 0.33 M toluene solution in 51% yield according to the representative procedure for the synthesis and handling of aliphatic diazoalkanes from 0.310 g (0.927 mmol) of methyl 3-((2-(triisopropylsilyl)hydrazono)-methyl)benzoate. Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*Dimethyl 3,3′-(2-Oxopropane-1,3-diyl)dibenzoate (**22a**).* Prepared according to the representative procedure above from 0.33 mmol of **21** (1.0 mL of a 0.33 M solution in toluene, 1.0 equiv) and 16.2 mg of $Sc(OTf)_3$ (0.033 mmol, 0.10 equiv). Diester **22a** was recovered as a colorless oil (48.5 mg, 90% yield) after flash chromatography (TLC R_f = 0.33 in 8:2 hexanes/ethyl acetate). IR (thin film): 2919 (m), 2863 (m), 1722 (m), 1711 (s), 1599 (w), 1562 (w), 1427 (w), 1413 (w), 1337 (m), 1309 (w), 1070 (w) 758 (w), 698 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, J = 7.6, 1.4 Hz, 1H), 7.82 (s, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.34 (dd, J = 6.1, 1.5 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 166.9, 134.2, 134.1, 130.8, 130.8, 128.9, 128.6, 52.3, 49.1. HRMS (ESI+) calcd for $C_{19}H_{19}O_5^+$ $[M + H]^+$: 327.1232; found 327.1213.

*3,3′-(2-Oxopropane-1,3-diyl)dibenzoic Acid (**22b**).* A solution of **22a** (27.6 mg, 0.085 mmol) in 1:1 THF−water (0.05 M) was added to a 10 mL round-bottom flask containing a Teflon-coated stir bar and treated with LiOH (20.0 mg, 0.858 mmol, 10 equiv) as a solid in one portion. Upon dissolution of the base, the colorless solution was stirred for 4 h and diluted with 20 mL of a 1 N HCl solution. The contents of the reaction vessel were then poured into a separatory funnel and washed three times with 25 mL of CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford a light yellow solid. Purification by silica gel chromatography (TLC R_f = 0.30 in 9:1 CH_2Cl_2/methanol) provided 11.6 mg of diacid **22b** as a white solid in 42% yield. Spectral data were in agreement with that reported in the isolation literature.[24]

*2-(Diazomethyl)furan (**23**).* Prepared as a 1.72 M toluene solution in 37% yield from 0.451 g of (furan-2-ylmethylene)hydrazone (4.09 mmol) by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*1,3-Di(furan-2-yl)propan-2-one (**24**).* Prepared according to the representative procedure above from 0.34 mmol of 2-(diazomethyl)-furan (**23**) (0.20 mL of a 1.72 M solution in toluene, 1.0 equiv) and 16.7 mg of $Sc(OTf)_3$ (0.034 mmol, 0.10 equiv). Purification by flash chromatography (TLC R_f = 0.30 in 92:8 hexanes/ethyl acetate) gave 23.8 mg of a colorless oil (74% yield). IR (thin film): 3121 (w),

2924 (w), 2853 (w), 1726 (s), 1598 (w), 1504 (m), 1384 (w), 1329 (w), 1147 (m), 1074 (w), 1011 (m), 913 (w), 806 (w), 734 (s), 599 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, J = 1.9, 0.8 Hz, 2H), 6.34 (dd, J = 3.1, 1.9 Hz, 2H), 6.19 (dd, J = 3.2, 0.7 Hz, 2H), 3.77 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 147.8, 142.4, 110.9, 108.7, 41.6. HRMS (ESI+) calcd for $C_{11}H_{11}O_3^+$ $[M + H]^+$: 191.0708; found 191.0725.

*2-(Diazomethyl)thiophene (**25**).* Prepared as a 0.35 M toluene solution in 45% yield from 0.353 g of (thiophen-2-ylmethylene)hydrazone (3.150 mmol) by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*1,3-Di(thiophen-2-yl)propan-2-one (**26**).* Prepared according to the representative procedure above from 0.14 mmol of 2-(diazomethyl)thiophene (0.40 mL of a 0.35 M solution in toluene, 1.0 equiv) and 8.0 mg of $Sc(OTf)_3$ (0.016 mmol, 0.12 equiv). Purification by flash chromatography (TLC R_f = 0.30 in 95:5 hexanes/ethyl acetate) provided 11.9 mg of a colorless oil (76% yield). IR (thin film): 3105 (w), 2921 (w), 2898 (w), 2854 (w), 1721 (s), 1612 (w), 1532 (w), 1435 (w), 1401 (w), 1317 (w), 1211 (w), 1079 (m), 851 (w), 696 (s), 537 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, J = 5.2, 1.2 Hz, 2H), 6.96 (dd, J = 5.2, 3.5 Hz, 2H), 6.87 (d, J = 3.5 Hz, 2H), 3.96 (d, J = 0.7 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 134.9, 127.3, 127.2, 125.5, 42.6. HRMS (ESI+) calcd for $C_{11}H_{11}S_2O^+$ $[M + H]^+$: 223.0251; found 223.0272.

*(Diazomethylene)dicyclopropane (**27**).* Prepared as a 0.63 M toluene solution in 28% yield according to the representative procedure for the synthesis and handling of aliphatic diazoalkanes from 0.516 g of (dicyclopropylmethylene)hydrazine (4.15 mmol). Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*1,1,3,3-Tetracyclopropylpropan-2-one (**28**).* Prepared according to the representative procedure above from 0.186 mmol of **27** (0.295 mL of a 0.63 M solution in toluene, 1.0 equiv) and 11.1 mg of $Sc(tmhd)_3$ (0.019 mmol, 0.10 equiv). Purification by flash chromatography (TLC R_f = 0.30 in 97.5:2.5 hexanes/ethyl acetate) gave 11.2 mg of **28** as a colorless oil (55% yield). IR (thin film): 3080 (w), 3006 (w), 2924 (m), 2854 (w), 1731 (s), 1463 (m), 1377 (w), 1272 (w), 1098 (m), 1020 (w), 998 (w), 958 (w), 932 (w), 856 (w), 820 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (t, J = 7.6 Hz, 2H), 0.94 (qt, J = 8.2, 5.1 Hz, 4H), 0.51−0.40 (m, 8H), 0.36−0.29 (m, 4H), 0.25−0.18 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 27.10, 20.8, 10.7. HRMS (ESI+) calcd for $C_{15}H_{23}O^+$ $[M + H]^+$: 219.1749; found 219.1744.

1-Bromo-2-(dibromomethyl)naphthalene. A 100 mL round-bottom flask equipped with a Teflon-coated stir bar was charged with 2.21 g (10.0 mmol) of 1-bromo-2-methylnaphthalene, 4.45 g of *N*-bromosuccinimide (25.0 mmol, 2.5 equiv), and 0.33 g of azobisisobutyronitrile (2.0 mmol, 0.20 equiv). The flask was outfitted with a reflux condenser, evacuated, and backfilled with nitrogen. The reactants were dissolved in benzene (35 mL, 0.30 M) and stirred at reflux for 24 h. The reaction mixture was then cooled to 23 °C, transferred to a separatory funnel, and washed three times with 25 mL of saturated sodium bisulfite. In each case, the aqueous wash was back-extracted with 5 mL of CH_2Cl_2, and this rinse fraction was added to the organic layer. After drying over sodium sulfate, filtering, and concentrating, the crude product was purified by passage through a pad of silica gel (TLC R_f = 0.35 in 98:2 hexanes/ethyl acetate) to give 3.61 g of the tribromide as a yellow solid (96% yield). Characterization data for this material have been reported previously.[75]

1-Bromo-2-naphthaldehyde. A 200 mL round-bottom flask containing a Teflon-coated stir bar was covered with aluminum foil to exclude light and charged with 3.79 g of 1-bromo-2-(dibromomethyl)-naphthalene (10.0 mmol) and 3.34 g of silver(I) acetate (20.0 mmol, 2.0 equiv). The solids were dissolved in 16 mL of water, 33 mL of acetone, and 50 mL of ethanol (0.10 M, 1:2:3 ratio). After 24 h of stirring at 23 °C, the mixture was placed in a separatory funnel and washed with 100 mL of Et_2O. The organic layer was washed twice with 80 mL of saturated sodium chloride. After collecting the ether layer, it was dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.33 in 98:2 hexanes/ethyl acetate) gave 2.21 g of the aryl carboxaldehyde as a solid (95% yield). Characterization data for this material have been reported previously.[75]

((1-Bromonaphthalen-2-yl)methylene)hydrazone. In a 20 mL vial equipped with a Teflon-coated stir bar, 1-bromo-2-naphthaldehyde (0.710 g, 3.02 mmol, 1.0 equiv) was suspended in 0.50 mL of hydrazine hydrate (15 mmol, 5.0 equiv) and 6.0 mL of ethanol (0.50 M). After sealing the vial with a Teflon-lined screw cap, the heterogeneous mixture was stirred rapidly at 80 °C. After 2 h, the mixture was cooled to 23 °C and left stirring for 12 h out of convenience. The product was then extracted with three 5 mL volumes of $CHCl_3$. The pooled extracts were dried over sodium sulfate, filtered, and concentrated to afford 0.479 g (2.90 mmol, 96% yield) of a white solid. The hydrazone was >98% pure and consisted of a >98:2 *E*:*Z* mixture on the basis of ^{1}H NMR analysis.

*1-Bromo-2-(diazomethyl)naphthalene (**29**).* Prepared as a 0.25 M toluene solution in 85% yield from 0.252 g of ((1-bromonaphthalen-2-yl)-methylene)hydrazone (1.01 mmol) by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*1,3-Bis(1-bromonaphthalen-2-yl)propan-2-one (**30**).* Prepared by the representative procedure given above from 0.50 mmol of **29** (2.0 mL of a 0.25 M solution in toluene, 1.0 equiv) and 25 mg of $Sc(OTf)_3$ (0.051 mmol, 0.10 equiv). Purification by flash chromatography (TLC R_f = 0.30 in 95:5 hexanes/ethyl acetate) delivered 86.6 mg of **30** as a white solid in 74% yield; mp = 163 °C. IR (thin film): 3087 (w), 3052 (w), 1716 (s), 1603 (w), 1585 (w), 1488 (w), 1452 (w), 1392 (m), 975 (w), 822 (m), 760 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.60 (dd, J = 8.4, 6.9 Hz, 2H), 7.52 (dd, J = 8.4, 6.8 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.24 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 133.9, 132.8, 132.7, 128.7, 128.3, 128.0, 127.7, 127.6, 126.6, 125.3, 51.3. HRMS (ESI+) calcd for $C_{23}H_{17}Br_2O^+$ $[M + H]^+$: 466.9646; found 466.9625.

9-Methylphenanthrene. A solution of 5.00 g of 9-bromophenanthrene (19.4 mmol) in Et_2O (100 mL, 0.20 M) at 0 °C was treated with 10.7 mL of *n*-BuLi (2.0 M in hexanes, 21.4 mmol, 1.1 equiv) dropwise over 10 min. After the solution was warmed to 23 °C for 10 min and recooled to 0 °C, 3.52 mL of dimethyl sulfate (36.9 mmol, 1.9 equiv) was added dropwise over a 30 min period. The reaction mixture was then heated to reflux for 5 h. After being cooled to 23 °C, the reaction was quenched with 40 mL of ammonium hydroxide and transferred to a separatory funnel. The organic layer was washed three times with 50 mL of saturated sodium chloride and then collected, dried over sodium sulfate, filtered, and concentrated. The resulting solid was crystallized from hexanes to give 3.59 g of colorless needles (72% yield). Characterization data for this material have been reported previously.[76]

9-Bromo-10-methylphenanthrene. A 100 mL round-bottom flask equipped with a Teflon-coated stir bar and covered with aluminum foil to exclude light was charged with 2.44 g (12.7 mmol) of 9-methylphenanthrene and 2.71 g of *N*-bromosuccinimide (15.2 mmol, 1.2 equiv). The flask was flushed with nitrogen and sealed with a rubber septum. The reactants were dissolved in acetonitrile (21.2 mL, 0.6 M) for 24 h of stirring at 23 °C. At the end of the reaction period, 20 mL of 1 N sodium hydroxide was added with 10 min of stirring. The mixture was poured into a separatory funnel and extracted with three 25 mL volumes of CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give 3.10 g (90% yield) of bromide that was used directly in the next reaction without purification. Characterization data for this material have been reported previously.[76]

9-Bromo-10-(bromomethyl)phenanthrene. A 250 mL flask containing a Teflon-coated stir bar was charged with 3.10 g of 9-bromo-10-methylphenanthrene (11.4 mmol), 4.27 g of *N*-bromosuccinimide (24.0 mmol, 2.1 equiv), and 0.280 g of azobisisobutyronitrile (1.71 mmol, 0.15 equiv). The flask was outfitted with a reflux condenser, evacuated, and purged with nitrogen. The reactants were dissolved in benzene (60 mL, 0.2 M) and stirred at reflux for 24 h. The reaction mixture was then cooled to 23 °C, transferred to a separatory funnel, and washed three times with 50 mL of saturated sodium bisulfite. In each case, the aqueous wash was back-extracted with 15 mL of CH_2Cl_2, and this rinse fraction was added to the organic

layer. The solution was dried over sodium sulfate, filtered, and concentrated to give 3.91 g (98%) of dibromide that was directly used in the next reaction without purification. Characterization data for this material have been reported previously.[76]

(10-Bromophenanthren-9-yl)methanol. A 250 mL round-bottom flask containing a Teflon-coated stir bar and coated with aluminum foil to exclude light was charged with 4.12 g (11.0 mmol) of 9-bromo-10-(bromomethyl)phenanthrene, and 4.00 g of silver(I) acetate (24.2 mmol, 2.2 equiv). After the solids were dissolved in 10 mL of water, 30 mL of acetone, and 60 mL of ethanol (0.10 M, 1:2:3 ratio), the solution was stirred at 23 °C for 24 h. The reaction mixture was then transferred to a separatory funnel and washed with 100 mL of Et_2O. In turn, the organic layer was washed three times with 80 mL of saturated sodium chloride and dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography (TLC R_f = 0.33 in 9:1 hexanes/ethyl acetate) gave 2.94 g of a solid (93% yield). Characterization data for this material have been reported previously.[76]

10-Bromophenanthrene-9-carbaldehyde. A −60 °C solution of 0.22 mL of methyl sulfoxide (3.13 mmol, 1.10 equiv) in THF (20 mL) was treated with 0.26 mL of oxalyl chloride (2.99 mmol, 1.05 equiv) dropwise over 5 min. After 15 min of stirring, 0.820 g (2.84 mmol, 1.0 equiv) of (10-bromophenanthren-9-yl)methanol was added in 8 mL of THF. After 15 min, 0.84 mL of triethylamine (5.97 mmol, 2.1 equiv) was added, and the vessel was allowed to slowly warm to 23 °C. The mixture was diluted with 50 mL of water in a separatory funnel and extracted three times with 20 mL of ethyl acetate. The combined organic layers were washed three times with 30 mL of saturated sodium chloride before being dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.30 in 95:5 hexanes/ethyl acetate) gave 0.72 g of the benzylic aldehyde as a white solid (88% yield). Characterization data for this material have been reported previously.[76]

((10-Bromophenanthren-9-yl)methylene)hydrazone. In a 2 dram glass vial equipped with a Teflon-coated stir bar, 0.190 g of 10-bromophenanthrene-9-carbaldehyde was suspended in 0.150 mL of hydrazine hydrate (3.33 mmol, 5.0 equiv) and ethanol (1.5 mL, 0.50 M). The vial was sealed with a Teflon-lined screw cap, and the mixture was stirred rapidly with heating at 80 °C. After 2 h, the mixture was cooled to 23 °C for 12 of stirring. The product was then extracted with three 5 mL volumes of $CHCl_3$. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 0.197 g of a white solid (99% yield). The hydrazone was >98% pure and consisted of a >98:2 *E*:*Z* mixture based on ^{1}H NMR analysis.

*9-Bromo-10-(diazomethyl)phenanthrene (**31**).* Prepared as a 0.42 M toluene solution in 81% yield from 0.200 g of ((10-bromophenanthren-9-yl)methylene)hydrazone (0.668 mmol) by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

2-(10-Bromophenanthren-9-yl)acetaldehyde. The predominant product when using the representative procedure given above with 0.110 mmol of **31** (0.262 mL of a 0.42 M solution in toluene, 1.0 equiv) and 5.4 mg of $Sc(OTf)_3$ (0.011 mmol, 0.10 equiv). Purification by flash chromatography (TLC R_f = 0.35 in 9:1 hexanes/ethyl acetate) gave 28.0 mg of the product as a white solid in 85% yield; mp = 198 °C. IR (thin film): 3068 (w), 2923 (w), 2850 (w), 2723 (w), 1721 (s), 1488 (w), 1445 (w), 753 (s), 720 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, J = 1.9 Hz, 1H), 8.65 (dd, J = 8.2, 1.4 Hz, 1H), 8.62 (d, J = 9.5 Hz, 1H), 8.41 (dd, J = 7.5, 2.1 Hz, 1H), 7.84 (dd, J = 8.1, 1.0 Hz, 1H), 7.64−7.60 (m, 3H), 7.58−7.53 (m, 1H), 4.52 (d, J = 1.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 131.6, 131.3, 130.1, 130.6, 129.2, 128.03, 128.01, 127.9, 127.4, 127.1, 125.00, 123.6, 122.9, 49.1. HRMS (ESI+) calcd for $C_{16}H_{12}BrO^+$ $[M + H]^+$: 299.0072; found 299.0050.

*1,3-Bis(10-bromophenanthren-9-yl)propan-2-one (**32**).* Prepared according to the general procedure given below for the synthesis of dissymmetric ketones from 45.6 mg of 2-(10-bromophenanthren-9-yl)acetaldehyde (0.152 mmol) and 0.168 mmol of **31** (0.4 mL of a 0.42 M solution in toluene, 1.10 equiv) with 8.3 mg of $Sc(OTf)_3$ (0.017 mmol, 0.10 equiv) in 1.8 mL of toluene (0.10 M). Purification by flash chromatography (TLC R_f = 0.35 in 9:1 hexanes/ethyl acetate) gave 57.8 mg of **32** as a white solid in 67% yield; mp = 249 °C. IR (thin film): 3073 (w), 2954 (w), 2923 (w), 2852 (w), 1712 (s), 1488 (m), 1444 (m), 1333 (w), 1066 (w), 1050 (w), 901 (w), 749 (s), 718 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 8.2 Hz, 2H), 8.69 (dd, J = 6.4, 3.1 Hz, 2H), 8.48 (dd, J = 7.6, 2.0 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.71−7.65 (m, 6H), 7.53 (t, J = 8.3 Hz, 2H), 4.73 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.9, 131.7, 131.3, 130.7, 130.5, 130.1, 129.2, 127.9, 127.8, 127.7, 127.2, 127.1, 125.3, 123.5, 122.8, 48.8. HRMS (ESI+) calcd for $C_{31}H_{20}Br_2ClO^-$ $[M + Cl]^-$: 602.9549; found 602.9578.

Diphenyl Diazomethane. Prepared as a 0.89 M toluene solution in 85% yield from 1.82 g (10.0 mmol) of benzophenone by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

*2,2-Diphenylacetaldehyde (**33**).* The predominant product if using the representative procedure given above with 0.178 mmol of diphenyl diazomethane (0.200 mL of a 0.89 M solution, 1.0 equiv) and 8.9 mg of $Sc(OTf)_3$ (0.018 mmol, 0.10 equiv). Purification by flash chromatography (TLC R_f = 0.30 in 97.5:2.5 hexanes/ethyl acetate) gave 13.8 mg of monoinsertion product as a colorless oil in 79% yield. Characterization data for this material have been reported previously.[77]

*1-Diazo-1,2,3,4-tetrahydronaphthalene (**34**).* Prepared as a 0.37 M toluene solution in 80% yield from 55.0 mg (0.343 mmol) of α-tetralone hydrazone by the known procedure.[29] Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

Representative Procedure for the Synthesis of a Dissymmetric Ketone from Two Different Diazoalkanes. *2,2-Diphenyl-1-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanone (**35**).* A stirring suspension of 38.2 mg (0.195 mmol) of 2,2-diphenylacetaldehyde and 9.8 mg of $Sc(OTf)_3$ (0.020 mmol, 0.10 equiv) in 2.0 mL toluene at −78 °C was treated with 0.214 mmol of 1-diazo-1,2,3,4-tetrahydronaphthalene (0.578 mL of a 0.37 M in solution in toluene, 1.1 equiv). After being stirred for 10 min at −78 °C, the reaction mixture was diluted with 20 mL of Et_2O, poured into a separatory funnel, and washed three times with 20 mL of water and once with 20 mL of saturated sodium chloride before being dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.33 in 97.5:2.5 hexanes/ethyl acetate) afforded 49.7 mg of **35** as a white solid in 78% yield; mp = 81 °C. IR (thin film): 3059 (m), 3026 (m), 2936 (m), 2867 (w), 1715 (s), 1658 (m), 1598 (w), 1494 (m), 1448 (m), 1317 (w), 1277 (m), 1075 (w), 1044 (w), 941 (w), 919 (w), 743 (m), 701 (s), 638 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, J = 8.2, 1.1 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.33 (dd, J = 9.1, 5.6 Hz, 2H), 7.28 (d, J = 2.3 Hz, 2H), 7.21 (dd, J = 6.4, 4.7 Hz, 2H), 7.12 (d, J = 5.7 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 5.35 (s, 1H), 4.06 (t, J = 6.3 Hz, 1H), 2.75 (dd, J = 13.7, 6.9 Hz, 2H), 2.11−1.93 (m, 2H), 1.77 (dd, J = 74.1, 4.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.4, 139.1, 138.5, 138.1, 137.8, 133.6, 132.6, 130.3, 129.8, 129.6, 129.3, 129.1, 129.0, 128.7, 128.5, 127.5, 127.2, 127.1, 126.0, 62.0, 53.2, 29.3, 26.2, 20.6. HRMS (ESI+) calcd for $C_{24}H_{23}O^+$ $[M + H]^+$: 327.1749; found 327.1775.

(Diazomethylene)dicyclohexane. Made as a 0.42 M toluene solution in 48% yield according to the representative procedure for the synthesis and handling of aliphatic diazoalkanes from 0.510 g (2.62 mmol) of dicyclohexyl ketone. Used immediately after preparation, otherwise stored cold at −78 °C.

*2,2-Dicyclohexylacetaldehyde (**36**).* The predominant product when the representative procedure above is run with 1.36 mmol of (diazomethylene)dicyclohexane (3.24 mL of a 0.42 M solution in toluene, 1.0 equiv) and 66.9 mg of $Sc(OTf)_3$ (0.136 mmol, 0.10 equiv). Purification by flash chromatography (TLC R_f = 0.30 in 98:2 hexanes/ethyl acetate) gave 129 mg of **36** as a colorless oil (91% yield). IR (thin film): 2923 (s), 2851 (m), 1721 (m), 1447 (w), 991 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (d, J = 4.6 Hz, 1H), 1.89−1.57 (m, 13H), 1.35−1.07 (m, 6H), 1.10−0.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 63.2, 35.7, 30.2, 26.7, 26.6.

HRMS (ESI+) calcd for $C_{14}H_{25}O^+$ [M + H]$^+$: 209.1905; found 209.1906.

*1,1-Dicyclohexyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butan-2-one (**38**).* Prepared according to the general procedure given above for the synthesis of a dissymmetric ketone from 25.1 mg of 2,2-dicyclohexylacetaldehyde (**36**) (0.120 mmol), 0.132 mmol of 4-(2-diazoethyl)-2,2-dimethyl-1,3-dioxolane (0.281 mL of a 0.47 M solution in toluene, 1.1 equiv), 7.1 mg of Sc(tmhd)$_3$ (0.012 mmol, 0.10 equiv), and 1.2 mL of toluene (0.10 M). Purification by silica gel chromatography (TLC R_f = 0.30 in 97.5:2.5 hexanes/ethyl acetate) afforded 27.5 mg of **38** as a colorless oil (68% yield). IR (thin film): 2920 (s), 2874 (m), 1719 (s), 1420 (w), 1347 (w), 1237 (w), 1009 (w), 984 (w), 955 (w), 928 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11−4.09 (m, 1H), 3.64 (dd, J = 8.3, 6.0, 1 H), 3.58 (dd, J = 8.3, 6.7, 1H), 2.53−2.66 (m, 2H), 2.38−2.35 (m, 1H), 1.89−1.59 (m, 14H), 1.42 (s, 3H), 1.37 (s, 3H) 1.35−1.07 (m, 6H), 1.12−0.90 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.3, 108.8, 69.3, 63.2, 39.8, 35.6, 30.2, 29.9, 27.6, 26.9, 26.7, 26.6, 25.8. HRMS (ESI+) calcd for $C_{21}H_{37}O_3^+$ [M + H]$^+$: 337.2743; found 337.2743.

(S)-Methyl 1-Benzylpyrrolidine-2-carboxylate. Prepared in accordance with a known procedure[78] in which AcCl (9.26 mL, 130 mmol) was added dropwise with stirring to a 0 °C solution of (*S*)-proline (5.00 g, 43.4 mmol) in MeOH (80 mL). Upon addition, the ice bath was removed and the stirring was continued for 15 h at 23 °C. Volatile organics were then removed, and the residual oil was redissolved in dry MeCN (70 mL). Et_3N (18.0 mL, 130 mmol) and BnBr (6.20 mL, 52.1 mmol, 1.2 equiv) were added to give a white suspension. After 12 h of stirring at 23 °C, the MeCN was evaporated and the residue was partitioned between saturated NH_4Cl (200 mL) and Et_2O (200 mL) in a separatory funnel. The phases were separated, and the aqueous layer was washed twice with 40 mL of Et_2O. The pooled organic layers were washed with one volume of saturated NaCl, dried over $MgSO_4$, and concentrated. Purification by silica gel chromatography (TLC R_f = 0.30 in 92:8 hexanes/ethyl acetate) gave 6.37 g of a colorless oil (69% yield). Spectroscopic data were in full agreement with values reported previously.[79]

(S)-1-Benzyl-2-pyrrolidinemethanol. To a solution of LAH (0.570 g, 15.1 mmol, 1.1 equiv) in THF (10 mL) at 0 °C was added (*S*)-methyl 1-benzylpyrrolidine-2-carboxylate (3.00 g, 13.7 mmol, 1.0 equiv) in THF (25 mL) dropwise with rapid stirring. After being warmed slowly to 23 °C and stirred for 6 h, the mixture was diluted with 15 mL of Et_2O, transferred to a separatory funnel, and washed with 50 mL volumes of saturated NH_4Cl and saturated NaCl. Before being discarded, the aqueous washes were back-extracted with 50 mL of Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 2.46 g of a colorless oil (12.9 mmol, 94% yield). The product's spectroscopic data were in agreement with that reported in the literature,[80] and it was used without further purification.

*(S)-1-Benzylpyrrolidine-2-carbaldehyde (**41a**).* Prepared in accordance with a known procedure[81] by adding a CH_2Cl_2 solution (11 mL, 1.5 M) of $(COCl)_2$ (1.45 mL, 16.6 mmol, 1.5 equiv) dropwise to a solution of DMSO (2.18 mL, 32.9 mmol, 3.0 equiv) in CH_2Cl_2 (22 mL, 1.5 M) at −78 °C. After stirring was continued at this temperature for 45 min, a CH_2Cl_2 (18 mL, 0.5 M) solution of (*S*)-1-benzyl-2-pyrrolidinemethanol (2.0 mL, 11 mmol) was added slowly over 10 min. After being stirred for 20 additional min at −78 °C, Et_3N (6.16 mL, 43.9 mmol, 4.0 equiv) was added and the reaction was allowed to warm slowly to 0 °C and stirred for 2 h. The mixture was diluted with 50 mL of CH_2Cl_2, transferred to a separatory funnel, and washed with 100 mL each of saturated $NaHCO_3$ and NaCl. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and directly concentrated to give 1.89 g of a colorless oil (9.98 mmol, 91% yield) that proved to be >98% pure by ^{1}H NMR analysis and was used without further purification. If possible, the compound should be used promptly as it undergoes slow decomposition in solution at 23 °C.

(S)-1-Benzyl-2-((2-triisopropylsilyl)hydrazono)methyl)pyrrolidine. Prepared by the representative procedure given above for the synthesis and handling of aliphatic diazoalkanes involving a slow, 2 h addition of triisopropylsilylhydrazine (0.780 g, 4.19 mmol, 1.5 equiv) to a solution of **41a** (0.530 g, 2.79 mmol) in THF (4.0 mL, 0.7 M) containing flame-dried 4 Å molecular sieves (0.53 g, 1:1 w/w) at 0 °C. Upon complete addition, the suspension was warmed to 23 °C and stirred rapidly under nitrogen for 36 h, at which time an NMR aliquot showed the absence of starting material. The mixture was filtered through cotton (with 2 mL of Et_2O as a rinse) and concentrated. The resulting 1.00 g of colorless oil (>99% yield) was used immediately without further purification.

*(S)-1-Benzyl-2-(diazomethyl)pyrrolidine (**42a**).* The following pilot-scale oxidation and esterification was used to determine if any loss in enantiopurity occurred during elaboration of **42a** from (*S*)-1-benzyl-2-pyrrolidinemethanol. Gratifyingly, no racemization of the proline-derived stereocenter occurs for batches of **42a** derived from either a Swern or Pb(IV)-based oxidation protocol. The former was chosen for scale-up even though the yield of diazoalkane was reproducibly 2−3% lower. A THF solution (4.0 mL, 0.040 M) of (*S*)-1-benzyl-2-((2-triisopropylsilyl)hydrazono)methyl)pyrrolidine (0.055 g, 0.154 mmol) was treated with TBAF (0.155 mL of a 1.0 M solution, 0.155 mmol, 1.0 equiv) at 0 °C with rapid stirring. After 10 min of stirring at 0 °C, the THF was removed under reduced pressure. Prior to deprotection of the hydrazone, a 1.0 M solution of $(COCl)_2$ (0.021 mL, 0.23 mmol, 1.5 equiv) in CH_2Cl_2 was added dropwise to a stirring solution of DMSO (0.031 mL, 0.46 mmol, 3.0 equiv) in CH_2Cl_2 (0.3 mL, 1.5 M) at −78 °C. After being stirred at this temperature for 45 min, the freshly prepared free hydrazone was slowly introduced over 10 min as a solution in 0.30 mL of CH_2Cl_2. The mixture was stirred for 20 min at −78 °C before Et_3N (0.86 mL, 0.62 mmol, 4.0 equiv) was added by syringe. After slow warming to 0 °C and 30 min of additional stirring, the reaction mixture was transferred to a separatory funnel and washed with 5 mL volumes of saturated $NaHCO_3$ and NaCl. The CH_2Cl_2 layer was then dried over Na_2SO_4, filtered, and concentrated under high vacuum at low temperature. These operations gave the neat diazoalkane as a yellow oil. After dissolution in 0.10 mL of toluene and esterification with 2-fluorobenzoic acid as described above, the titer was determined to be 0.50 M, corresponding to a 33% yield from the aldehyde **42a** (four steps). Diazoalkane **42a** was also made reliably in 36% yield by the general procedure above for the synthesis and handling of aliphatic diazoalkanes with $Pb(OAc)_4$ as the oxidant and starting from 1.35 g (3.75 mmol) of the TIPS-hydrazone. The diazoalkane was used immediately after its synthesis, otherwise stored cold at −78 °C.

*(S)-(1-Benzylpyrrolidin-2-yl)methyl 2-Fluorobenzoate (**43**).* For an appreciable amount of the *o*-fluorobenzoate, the esterification reaction was conducted as follows. A 400 μL aliquot of the 0.45 M diazoalkane stock solution (0.18 mmol) was added to a solution of 2-fluorobenzoic acid (25.2 mg, 0.18 mmol, 1.0 equiv) in Et_2O (0.50 mL, 0.36 M) at −45 °C dropwise by syringe. The cooling bath was removed, and upon slow warming from −45 °C, the reaction mixture became colorless and nitrogen evolution was observed. Direct concentration of the reaction mixture and purification by flash chromatography (TLC R_f = 0.30 in 95:5 hexanes/ethyl acetate) gave 56 mg of the ester as a viscous, colorless oil (99% yield, >99% ee based on chiral SFC, trace provided as Supporting Information). $[\alpha]_D^{23}$ = −59.6 (c = 0.80 g·cm^{-3} in $CHCl_3$). IR (thin film): 2950 (m), 2843 (w), 2779 (m), 1712 (s), 1612 (m), 1488 (m), 1454 (m), 1293 (s), 1247 (s), 1228 (m), 1157 (m), 1124 (m), 1081 (s), 1033 (s), 967 (w), 754 (s), 691 (w), 655 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (td, J = 7.6, 1.8 Hz, 1H), 7.55−7.49 (m, 1H), 7.38 (d, J = 7.0 Hz, 2H), 7.33 (t, J = 7.3 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.21 (td, J = 7.7, 1.1 Hz, 1H), 7.15 (ddd, J = 10.7, 8.4, 1.0 Hz, 1H), 4.37 (qd, J = 11.0, 5.7 Hz, 2H), 4.21 (d, J = 13.1 Hz, 1H), 3.49 (d, J = 13.1 Hz, 1H), 3.06−2.94 (m, 2H), 2.32 (ddd, J = 9.1, 6.0, 2.3 Hz, 1H), 2.12−2.01 (m, 1H), 1.87 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (d, J = 2.9 Hz), 162.1 (d, J = 206.8 Hz), 139.7, 134.5 (d, J = 7.1 Hz), 132.2 (d, J = 2.9 Hz), 128.8, 128.1, 126.9, 124.0 (d, J = 3.2 Hz), 119.0, 118.9, 117.1, 116.9, 68.0, 61.9, 59.5, 54.5, 28.7, 23.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ 110.2. HRMS (ESI+) calcd for $C_{19}H_{21}FNO_2^+$ [M + H]$^+$: 314.1556; found 314.1564.

1,3-Bis((S)-1-benzylpyrrolidin-2-yl)propan-2-one. Prepared according to the representative procedure for the bidirectional synthesis of ketones from 0.156 mmol of (*S*)-1-benzyl-2-(diazomethyl)pyrrolidine

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42a (0.75 mL of a 0.21 M toluene solution). Due to concern that the ketone might racemize during exposure to silica gel, its enantiopurity was directly assayed by SFC (>98% ee, trace provided as Supporting Information), and it was moved onto the natural product as is. Still, in other experiments, the material was purified to gauge homologation efficiency. Purification by silica gel chromatography (TLC R_f = 0.30 in 70:30 hexanes/ethyl acetate) gave 31 mg of a colorless oil (58% yield). $[\alpha]^{23}_D$ = −35.2 (c = 1.53 g·cm^{-3}, in $CHCl_3$). IR (thin film): 3086 (m), 3058 (w), 3027 (m), 2966 (m), 2872 (m), 1711 (s), 1601 (m), 1495 (m), 1444 (m), 1370 (w), 1317 (w), 1262 (w), 1221 (w), 1167 (m), 1078 (m), 1043 (w), 1029 (m), 908 (w), 807 (w), 718 (w), 697 (s), 615 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.28 (m, 10H), 3.90 (d, J = 13.1 Hz, 2H), 3.47 (d, J = 13.1 Hz, 2H), 3.01 (dd, J = 8.8, 7.4 Hz, 2H), 2.88−2.80 (m, 2H), 2.48−2.36 (m, 4H), 2.36−2.25 (m, 2H), 2.17−2.04 (m, 2H), 1.92−1.80 (m, 2H), 1.80−1.68 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.5, 138.1, 129.2, 128.5, 127.3, 62.9, 61.5, 56.4, 53.0, 35.1, 25.0. HRMS (ESI+) calcd for $C_{25}H_{33}N_2O^+$ $[M + H]^+$: 377.2593; found 377.2612.

*(−)-Dihydrocuscohygrine (**44**).* To a suspension of Pd/C (10% w/w) in 1.0 mL of MeOH was added unpurified 1,3-bis((*S*)-1-benzylpyrrolidin-2-yl)propan-2-one (0.156 mmol theoretical) in MeOH (2.6 mL, 0.060 M based on theoretical) through a cannula under N_2 atmosphere. The reaction mixture was purged with H_2 three times from a balloon, and the 1 atm environment was maintained for 16 h of stirring at 23 °C. The catalyst was removed by filtration through a pad of neutral Al_2O_3 with two 0.5 mL volumes of MeOH to rinse the filter cake. The filtrate was directly collected in a 5 mL round-bottom flask containing a stirring solution of 29.5 μL of formic acid (0.782 mmol, 5.0 equiv) in a 37% formaldehyde solution (0.23 mL, 20 equiv) at 23 °C. The resulting light yellow solution was heated at 80 °C for 6 h. After cooling to 23 °C, the reaction mixture was diluted with 15 mL of $CHCl_3$, transferred to a separatory funnel, and washed three times with 15 mL volumes from a cold solution of 1.0 N NaOH. The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated to an oil. Purification by silica gel chromatography (TLC R_f = 0.38 in 5:4:1 hexanes/DCM/Et_2NH) afforded 7.6 mg of (−)-dihydrocuscohygrine (**44**) as a colorless oil that quickly turns yellow upon standing at 23 °C (0.034 mmol, 43% yield over three steps). Enantiomeric purity for the natural product was determined by chiral gas chromatography in comparison to authentic racemic material (99:1 er in trace provided as Supporting Information, Chiraldex BDM column, 15 psi, 250 °C). $[\alpha]_D^{23}$ = −102 (c = 0.76 g·cm^{-3}, acetone). IR (thin film): 3254 (b), 2937 (s), 2839 (m), 2781 (s), 1658 (w), 1547 (w), 1543 (s), 1370 (m), 1352 (w), 1289 (w), 1209 (m), 1110 (m), 1037 (s), 957 (w), 901 (m), 827 (m), 745 (w), 700 (w), 575 (w), 459 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12−4.03 (m, 1H), 3.07 (t, J = 7.8 Hz, 2H), 2.41−2.36 (m, 2H), 2.35 (s, 6H), 2.14 (td, J = 9.4, 7.7 Hz, 2H), 2.00−1.89 (m, 2H), 1.83−1.76 (m, 2H), 1.75−1.65 (m, 4H), 1.63−1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.4, 64.5, 57.3, 41.0, 39.4, 30.3, 23.1. HRMS (ESI+) calcd for $C_{13}H_{27}N_2O^+$ $[M + H]^+$: 227.2123; found 227.2134.

(±)-Cuscohygrine. Following the procedure of Stapper and Blechert,[66] a solution of (−)-dihydrocuscohygrine (**44**) (7.0 mg, 0.031 mmol) in acetone (0.20 mL, 0.15 M) was treated with freshly prepared Jones' reagent (0.20 g of CrO_3, 0.178 mL of H_2SO_4, and 1.08 mL of water) at 0 °C and stirred for 1 h at this temperature. At this point, the reaction mixture was quenched with 10 mL of saturated $NaHCO_3$, transferred to a separatory funnel, and washed three times with 10 mL of ice cold $CHCl_3$. The pooled organic layers were washed with 25 mL of a 30% KOH solution precooled to −20 °C, dried over Na_sSO_4, filtered, and concentrated to an oil. Purification by silica gel chromatography (TLC R_f = 0.26 in 5:4:1 hexanes/DCM/Et_2NH) gave 5.6 mg of cuscohygrine as a colorless oil (0.025 mmol, 81% yield). This material, which proved to be racemic as a function of a known epimerization mechanism,[69,70] had the following spectral properties. IR (thin film): 3386 (m), 2924 (s), 2853 (m), 2780 (m), 1712 (s), 1456 (m), 1375 (m) 1210 (w), 1115 (w), 1031 (w), 966 (w), 906 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13−3.04 (m, 2H), 2.88−2.79 (m, 2H), 2.68−2.43 (m, 4H), 2.33 (s, 6H), 2.27−2.18 (m, 2H), 2.16−2.01 (m, 2H), 1.86−1.66 (m, 4H), 1.50−1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 208.6, 62.0, 61.9, 56.8, 48.2, 48.1, 40.6, 40.6, 31.4, 22.2. HRMS (ESI+) calcd for $C_{13}H_{25}N_2O^+$ $[M + H]^+$: 225.1967; found 225.1960.

*(S)-1-Methylpyrrolidine-2-carbaldehyde (**41b**).* Prepared in accordance with a known procedure[82] by adding $(COCl)_2$ (0.179 mL, 2.05 mmol, 1.03 equiv) dropwise to a stirring solution of DMSO (0.150 mL, 2.11 mmol, 1.06 equiv) in CH_2Cl_2 (3.0 mL, 0.70 M) at −78 °C. After being stirred for 20 min at this temperature, the homogeneous solution was warmed to −50 °C and a CH_2Cl_2 (1.0 mL, 2.0 M) solution of (*S*)-1-methyl-2-pyrrolidinemethanol (230 mg, 2.0 mmol) was added as a gentle stream down the walls of the reaction flask for adequate precooling. The mixture became turbid after being stirred for 30 min at −50 °C. The flask was cooled to −78 °C, and Et_3N (0.307 mL, 2.20 mmol, 1.10 equiv) was added dropwise to the center of the stirring mixture by syringe. After 30 min of stirring at −60 °C, a cloudy precipitate had formed. Pentane (5.0 mL) was then added to the reaction mixture for 10 min of stirring. The septum was then removed in preparation for filtration through Celite with multiple pentane rinses. The volatiles were then removed under reduced pressure, giving 0.196 g of a colorless oil (1.73 mmol, 86%). The material was kept under nitrogen atmosphere at all times and quickly transformed to its corresponding TIPS-hydrazone without any further purification. The compound had to be used immediately since it undergoes slow decomposition in solution at 23 °C.

(S)-1-Methyl-2-((2-triisopropylsilyl)hydrazono)methyl)pyrrolidine. Prepared by the representative procedure above for synthesis and handling of aliphatic diazoalkanes involving a 2 h addition of triisopropylsilylhydrazine (0.489 g, 2.59 mmol, 1.5 equiv) to a 0 °C solution of (*S*)-1-methylpyrrolidine-2-carbaldehyde (0.196 g, 1.73 mmol) in THF (3.5 mL, 0.5 M) containing flame-dried 4 Å molecular sieves (0.20 g, 1:1 w/w). Upon completion of the addition, the suspension was warmed to 23 °C and stirred rapidly under N_2 for 36 h, at which time an NMR aliquot showed the absence of starting material. The mixture was filtered through cotton (with 2 mL of Et_2O as a rinse) and concentrated. The resulting 0.485 g of colorless oil (99% yield) was used quickly without further purification.

*(S)-1-Methyl-2-(diazomethyl)pyrrolidine (**42b**).* Prepared as a 0.33 M toluene solution in 23% yield by following the general procedure for the synthesis and handling of aliphatic diazoalkanes with 0.485 g of (*S*)-1-methyl-2-((2-triisopropylsilyl)hydrazono)methyl)-pyrrolidine (1.71 mmol). Used in a reaction immediately after its preparation, otherwise stored cold at −78 °C.

(±)-Cuscohygrine. Prepared according to the representative procedure for the bidirectional synthesis of ketones starting with 0.410 mmol of (*S*)-1-methyl-2-(diazomethyl)pyrrolidine (1.24 mL of a 0.33 M solution in toluene) and 19.6 mg of $Sc(OTf)_3$ (0.041 mmol, 0.10 equiv). Purification by column chromatography over neutral alumina (TLC R_f = 0.31 in 5:4:3 in hexanes/CH_2Cl_2/Et_3N) gave 8.3 mg of a colorless oil (18% yield). Characterization data were identical to that reported in the literature[66] and that obtained above by Jones oxidation of (−)-dihydrocuscohygrine.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and analytical SFC or GC traces to validate enantiopurity. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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■ REFERENCES

(1) (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258−3260.
(2) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131−1134.
(3) Murata, H.; Ishitani, H.; Iwamoto, M. *Tetrahedron Lett.* **2008**, *49*, 4788−4791.
(4) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532−8533.
(5) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479−1492.
(6) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926−10940.
(7) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426−12427.
(8) A review on catalytic carbon C−H insertion reactions based on α-diazo ester and diazocarbonyl reagents: Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704−724.
(9) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417−424.
(10) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434−2435.
(11) Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 878−879.
(12) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202−3205.
(13) Moebius, D. C.; Dabrowski, J. A.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. *Org. Lett.* **2010**, *12*, 3598−3601.
(14) Rendina, V. L.; Moebius, D. C.; Kingsbury, J. S. *Org. Lett.* **2011**, *13*, 2004−2007.
(15) Rendina, V. L.; Kaplan, H. Z.; Kingsbury, J. S. *Synthesis* **2012**, 686−693.
(16) Gutsche, C. D. *Org. React.* **1954**, *8*, 364−429.
(17) Hauptmann, S.; Hirschberg, K. *J. Prakt. Chem.* **1966**, *34*, 272.
(18) Gutsche, C. D.; Redmore, D. In *Carbocyclic Ring Expansion Reactions*; Hart, H., Karabatsos, G. J., Eds.; Academic Press: New York, 1968; pp 81−98.
(19) Mullin, S.; Mani, N.; Grossman, T. H. *Antimicrob. Agents Chemother.* **2004**, 4171−4176.
(20) Minderman, H.; O'Loughlin, K. L.; Pendyala, L.; Baer, M. R. *Clin. Cancer Res.* **2004**, *10*, 1826−1834.
(21) Polydefkis, M.; Sirdofsky, M.; Hauer, P.; Petty, B. G.; Murinson, B.; McArthur, J. C. *Neurology* **2006**, *66*, 259−261.
(22) Cai, M.; Zhou, Y.; Wang, X.; Li, R.; Liao, X.; Ding, L. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 1931−1936.
(23) Wang, X.; Ma, Y.-Y.; Ding, K.-Y.; Ding, L. *Chinese Traditional and Herbal Drugs* **2010**, *41*, 340−342.
(24) Zhang, X.-P.; Liu, M.-S.; Zhang, J.-Q.; Kang, S.-L.; Pei, Y.-H. *J. Asian Nat. Prod. Res.* **2009**, *11*, 75−78.
(25) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855−2862.
(26) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961−3964.
(27) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17.
(28) A review on applications of two-directional strategies in natural products synthesis: Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213.
(29) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789−1792.
(30) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222−12223.
(31) Holton, T. L.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725−4729.
(32) For a thorough discussion on the longstanding complication of hydrazone instability, see: Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436−5445.
(33) Justo de Pomar, J. C.; Soderquist, J. A. *Tetrahedron Lett.* **2000**, *41*, 3285−3288.
(34) $PhI(O_2CCF_3)$ can be substituted for $Pb(OAc)_4$ with no impact on the yield of **2**, although the extract becomes contaminated with PhI.
(35) Informative details are posted in the Aldrich Technical Bulletin #AL-180: "Diazald®, MNNG, and Diazomethane Generators." This material is available under the 'Related Information' tab of the Search command at http://www.sigma-aldrich.com.
(36) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.
(37) Sammakia, T. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, U.K., 1995.
(38) Proctor, L. D.; Warr, A. J. *Org. Process Res. Dev.* **2002**, *6*, 884−992.
(39) Explosion of a supersaturated crystallizing solution was once observed: De Boer, T. J.; Backer, H. J. In *Organic Synthesis, Collective*; Rabjohn, N., Ed.; John Wiley and Sons: New York, 1963; Vol. *IV*, pp 250−252.
(40) Shankar, B. K. R.; Shechter, H. *Tetrahedron Lett.* **1982**, *23*, 2277−2279.
(41) Rendina, V. L.; Kingsbury, J. S. *J. Org. Chem.* **2012**, *77*, 1181−1185.
(42) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675−680.
(43) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38−54.
(44) Alexander, M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900−9901.
(45) For an early double Knoevenagel−inverse demand Diels−Alder approach to 9,10-disubstituted fluoranthenes, see: Scott, L. T.; Hashemi, M. M.; Meyer, D. T.; Warren, H. B. *J. Am. Chem. Soc.* **1991**, *113*, 7082−7084.
(46) Grimsdale, A. C.; Müllen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5592−5629 and references cited therein.
(47) Potter, R. G.; Hughes, T. S. *Org. Lett.* **2007**, *9*, 1187−1190.
(48) Potter, R. G.; Hughes, T. S. *Chem. Commun.* **2007**, 4665−4667.
(49) Jackson, E. A.; Steinberg, B. D.; Bancu, M.; Wakamiya, A.; Scott, L. T. *J. Am. Chem. Soc.* **2007**, *129*, 484−485.
(50) Omachi, H.; Segawa, Y.; Itami, K. *Acc. Chem. Res.* **2012**, *45*, 1378−1389.
(51) Scott, L. T.; Jackson, E. A.; Zhang, Q.; Steinberg, B. D.; Bancu, M.; Li, B. *J. Am. Chem. Soc.* **2012**, *134*, 107−110.
(52) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.
(53) Rodriquez, L.; Lu, N.; Yang, N.-L. *Synlett* **1990**, 227−228.
(54) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216.
(55) Gilman, H.; Catlin, W. E. *Org. Synth.* **1926**, *6*, 22.
(56) Reisch, H. A.; Bratcher, M. S.; Scott, L. T. *Org. Lett.* **2000**, *2*, 1427−1430.
(57) Andrusyszyn, P. M. Extending the Aryl Radical Cyclization Approach to Large Geodesic Polyarenes. Ph.D. Thesis, Boston College, 2002.
(58) Liebermann, C. *Ber.* **1889**, *2*, 675.
(59) Liebermann, C.; Cybulski, G. *Ber.* **1895**, *28*, 578.
(60) Turner, C. E.; Elsohly, M. A.; Hanus, L.; Elsohly, H. N. *Phytochemistry* **1981**, *20*, 1403−1405.
(61) El-Imam, Y. M. A.; Evans, W. C.; Plowman, T. *Phytochemistry* **1985**, *24*, 2285−2289.
(62) Christen, P.; Roberts, M. F.; Phillipson, J. D.; Evans, W. C. *Phytochemistry* **1995**, *38*, 1053−1056.
(63) Leete, E. *Phytochemistry* **1983**, *22*, 699.

(64) Novak, M.; Salemink, C. A.; Khan, I. *J. Ethnopharmacol.* **1984**, *10*, 261−274.
(65) Watson, E. S.; Murphy, J. C.; Elsohly, H. N.; Elsohly, M. A.; Turner, C. E. *Toxicol. Appl. Pharmacol.* **1983**, *71*, 1−13.
(66) Stapper, C.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 6456−6460.
(67) Yamauchi, T.; Hagiwara, S.; Higashiyama, K. *J. Org. Chem.* **2008**, *73*, 9784−9787.
(68) Icke, R. N.; Wisegarver, B. B.; Alles, G. A. *Org. Synth.* **1945**, *25*, 89.
(69) Brown, R. T. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; Wiley Interscience: New York, 1983; Vol. *25*, Part 4, pp 85−97.
(70) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027−2030.
(71) Pross, A.; Sternhill, S. *Aust. J. Chem.* **1970**, *23*, 989−1003.
(72) Lee, D. O.; Jensen, C. M. *J. Chem. Educ.* **2000**, *77*, 629.
(73) Potter, R. G.; Hughes, T. S. *J. Org. Chem.* **2008**, *73*, 2995−3004.
(74) Inaba, S.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373−1381.
(75) Bongui, J.; Elomri, A.; Cahard, D.; Tillequin, F.; Pfeiffer, B.; Pierre, A.; Seguin, E. *Chem. Pharm. Bull.* **2005**, *53*, 1540−1547.
(76) Lin, S.; Chen, Q.; You, T. *Synlett* **2007**, *13*, 2101−2105.
(77) Nagahara, S.; Maruoka, K.; Yamamoto, H. *Chem. Lett.* **1992**, *21*, 1193−1196.
(78) Trost, B. M.; Ito, H. Catalytic Compositions and Methods for Asymmetric Aldol Reactions. U.S. Patent 147367-A1, 2002.
(79) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442−444.
(80) Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737−2743.
(81) Deur, C. J.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1996**, *61*, 2871−2876.
(82) Cannon, J. G.; Milne, L. D. *J. Heterocycl. Chem.* **1976**, *13*, 686−689.