Published in final edited form as:

Nature. 2018 August ; 560(7718): 350–354. doi:10.1038/s41586-018-0391-9.

Building C(sp³)-rich Complexity by Combining Cycloaddition and C–C Cross Coupling Reactions

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Abstract

Prized for their ability to rapidly generate complexity in building new ring systems and stereocenters¹, cycloadditions have featured in numerous total syntheses² and are a key component in the education of chemistry students³. Similarly, C–C cross-coupling methods are integral to synthesis due to their programmability, modularity, and reliability⁴. Within the area of drug discovery, an overreliance on cross-coupling has led to a disproportionate representation of flat, sp²-rich architectures⁵. Despite the ability of cycloadditions to introduce multiple C(sp³) centres in a single step, they are less used⁶. This is likely due to a striking lack of modularity stemming from the idiosyncratic steric and electronic rules for each specific type of cycloaddition. Here, we demonstrate a strategy for taking the optimal features of these two essential transforms and combining them into one simple sequence to enable the modular, enantioselective, scalable, and programmable preparation of useful building blocks, natural products, and lead scaffolds for drug discovery.

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Author Contributions T.C., T.Q. and P.S.B. conceived the work. T.C., L.S.B., Y.L., J.T., D.K., I.B., S.A., C.B., J.C., M.S., H.F., F.G.F., H.C., L.H., T.Q. and P.S.B. designed the experiments and analyzed the data. T.C., L.S.B., Y.L., J.T., D.K., I.B., S.A., C.B. and J.C. performed the experiments. M.S., H.F., F.G.F., H.C. and L.H., performed experiments in Panel I. P.S.B. wrote the manuscript. T.C., L.S.B., Y.L., J.T., D.K., I.B., S.A., C.B., J.C. and T.Q. assisted in writing and editing the manuscript.

The authors declare no competing financial interests.

Data Availability

Metrical parameters for the structures of **11**, **19**, **23**, **25**, **28**, **44**, **45**, **49**, **65**, **C2**, **107**, **1•2HCl** and **118•2HCl** are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under reference numbers 1837572, 1837575, 1837577, 1837578, 1837579, 1937573, 1837574, 1937576, 1821880, 1821878, 1821879, 1825177 and 1838237, respectively. Data are available from the corresponding author on reasonable request.

Supplementary Information is available in the online version of the paper.

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Retrosynthetic analysis is built upon the strategic identification of the reactions (transforms) that offer the greatest potential to simplify target preparation (“T-goal”)³. To this end, the capacity for generating complex ring systems and multiple bonds with precise stereochemical control via cycloaddition is unmatched. In contrast, C–C cross couplings such as Heck, Suzuki, and Negishi reactions, capable of making only one bond at a time (most often between flat sp²-systems)⁴, are the most used C–C bond forming methods in the patent literature⁷. To understand this phenomenon, it is worthwhile to compare the features of these two diverse reaction classes (**Figure 1A**). Cycloadditions form two new sigma bonds generally through concerted pathways that follow precise rules for predicting stereo- and regiochemistry. This rapidly accesses complexity starting with specialized building blocks, designed to enable the reaction to take place cleanly⁸. On the other hand, C–C cross couplings form one new sigma bond between easily accessible building blocks using a transition metal catalyst to reliably and controllably produce new connections. What C–C cross coupling lacks in terms of complexity generation it makes up in the form of sheer reliability and modularity. These distinct features are illustrated by the syntheses of the alkaloid epibatidine (**1**, **Figure 1A**)⁹ and the commercial antihypertensive medicine Cozaar (**2**)¹⁰. **1**, coveted for its pronounced analgesic properties, has been prepared by total synthesis over sixty times (see SI section E for a complete listing). Of these, at least 31 have utilized cycloaddition chemistry as their key ring-constructing step. The vast majority of these approaches involve formation of the bridged pyrrolidine core followed by stepwise, and often lengthy, pyridine incorporation. Medicinal agent **2**, bereft of any stereogenic centers or topological complexity, was heralded as one of the first examples of a “blockbuster” drug. Both its discovery and eventual manufacture utilized C–C cross coupling (Ullmann and Suzuki) for the key bond cleavage^{11,12}. This facilitated both a convergent assembly and modularity that permitted the rapid exploration of hundreds of analogs. We therefore sought to combine the innate complexity-generation of cycloaddition with the simplicity and modularity of C–C coupling. When applied to structures such as **1**, this strategy would permit the rapid generation of analogs and when applied to medicinal programs such as **2**, it would allow for rapid exploration of otherwise challenging complex chemical space.

Building block **3**, of hypothetical value in medicinal chemistry, represents the manifestation of this idea (**Figure 1B**). Although its structure beckons for the use of a Diels–Alder (DA) reaction, the corresponding building blocks **4** and **5** are not electronically matched and therefore one would expect no reaction to take place. Even if a workable enantioselective DA could be invented to achieve this transform, the strategy would suffer from a lack of modularity. In order to solve this problem, one could envisage a vicinal dihaloethylene **6** in place of **5**, and a fumarate-type dienophile such as **7** could serve as a viable synthetic equivalent. The favorable matched electronics of the dienophile should allow for a facile DA and subsequent radical cross coupling (RCC). To address the enantioselectivity challenge, a combination of transforms was proposed (**Figure 1C**). Maleic anhydride was chosen as a surrogate for the hypothetical chiral (pseudo)dihalide **6** given its inexpensive nature, ready participation in most cycloaddition modes ([2+1], [2+2], [3+2], [4+2]), and known desymmetrization through chiral Lewis-base mediated hydrolysis. Such a sequence for generating complexity in a modular fashion would involve five simple steps: 1.

Cycloaddition to build a scaffold, 2. Desymmetrization to set absolute stereochemistry, 3. RCC to install a new C–C bond, 4. Hydrolysis, and 5. RCC to forge another new C–C bond. The known versatility of the RCC enables a range of functionalities to be installed, from aryl¹³ and heteroaryl¹⁴ systems to alkenes¹⁵, alkynes¹⁶ and alkyl groups¹⁷. We describe the preparation of >80 synthetic examples and multiple applications covering a range of natural products (including the synthesis of **1**) and real-world examples from industrial settings.

Studies commenced with the DA cycloaddition (**Figure 2A**) where a large variety (6) of enantiopure scaffolds could be produced in a simple modular fashion. First, scaffolds **A**₁–**A**₆ (**A**₂ is a DA adduct and all others are derived from DA/hydrogenation) were desymmetrized using Deng's conditions with either quinine or quinidine as Lewis-base to deliver mixed acid/esters in excellent enantioselectivity¹⁸. Next, the mono-acid substrate was subjected to successive Negishi^{13,15–17} and Suzuki¹⁴ type RCC reactions based on starting material availability or individual preferences. In this manner, some of the most simple and inexpensive DA products known (**A**₁ is \$38.54/mol and **A**₂ is \$9.52/mol) were transformed into enantiopure products of high value. Indeed, none of these entities can currently be prepared using a DA reaction (racemic or enantiopure) as in most cases the analogous DA would require both an electron-rich diene and electron-rich dienophile which is electronically unfavored. Furthermore, controlling the chemoselectivity when there are multiple alkenes present in the dienophile is challenging using tradition DA chemistry; however, with our method diverse alkenes and alkynes can be easily installed post-cyclization with excellent isomeric and geometrical purity (**12**, **15**, **19**, **21**, **25**, **31**). Typically scaffolds derived from DA-adducts **A**₁–**A**₆ have a clear retrosynthetic signature wherein the electron withdrawing groups on the dienophile have been homologated, alkylated, or degraded. Therefore, our approach allows access to previously unexplored chemical space of electron-rich, chiral, 1,2-disubstituted DA scaffolds. Using the tactical combination outlined above a virtually limitless array of substituents are now easily accessed including halogenated arenes, Lewis-basic heterocycles, α,β -unsaturated carbonyl groups, cyclopropanes, cyclobutanes, sulfur moieties, and alkenes. In the case of *exo* and *endo* isomers **A**₄ and **A**₅ (both commercially available), the products of the sequence were convergent to an identical product using the same coupling partners (**27** could be prepared from **A**₄ and **A**₅, respectively).

As shown in **Figure 2B–D**, the strategy outlined above could also be applied to [3+2], [2+2], and [2+1] cycloadditions. The vast scope observed with DA chemistry was also seen in these cases, accessing substituents such as substituted olefins, terminal alkynes, homoallyl groups, and heterocycles. Pyrrolidine-containing systems could be derived from simple building blocks **B**₁ and **B**₂ (accessed through dipolar cycloaddition)¹⁹ to furnish **64–82** in high *ee*. Quick access to pyrrolidine-containing drug scaffolds is useful as historically these have been extremely relevant to medicinal chemists with *ca.* 40 pharmaceuticals containing this motif²⁰. As with the DA adducts, none of these structures have been accessed before. Therefore, our approach serves as a modular entry to chiral variants of these coveted scaffolds. In a similar vein, enantiopure cyclopentenones derived from Pd-catalyzed TMM-based formal [3+2] cycloaddition adduct **B**₃²¹ were easily produced. Such structures are highly challenging to access in any other way. Scaffolds **C**₁ and **C**₂, representing entry to

[2+2]-derived systems, could be similarly processed. Modular access to enantiopure cyclobutanes is significant and useful given the strict electronic requirements for photochemical cycloaddition and the documented challenge in achieving general asymmetric induction²². Access to 1,2-disubstituted cyclobutanes (**83-86**, derived from **C**₁) compares favorably with photochemical approaches to such systems that frequently give inseparable racemic mixtures of regio- and diastereomers. Furthermore, access to tetrasubstituted, chiral cyclobutanes is highly useful as multiple families of dimeric and pseudodimeric cyclobutane natural products contain such structural motifs²³. Structures such as **87**, which would be otherwise extremely difficult to access through conventional photochemistry, can be easily prepared in enantiopure manner from maleic anhydride heterodimerization adducts such as **C**₂. Finally, the strategy outlined above when applied to [2+1] cycloadditions using scaffolds **D**₁ and **D**₂ is a significant departure from common retrosynthetic logic normally applied to such structures. Conventional approaches, usually involving late-stage cyclopropanation of an olefin, suffer from lack of enantiocontrol in the absence of directing groups or specialized carbenoid donors and complex catalysts²⁴. Structures **94** and **95** (**D**₂-derived) are particularly illustrative of this fact as it would be extremely challenging to access either of these in an enantioselective fashion with current synthetic technology (cyclopropanation or C–C cross coupling). As a testament to the power of this strategy to access diverse libraries, an additional 48 enantioriched compounds were synthesized in a similar manner (see Extended Data Figures for details).

To further demonstrate the potential of this approach to simplify synthesis, six applications are presented in natural product total synthesis and both early- and late-stage medicinal chemistry programs (**Figure 3E-J**). As mentioned above, alkaloid **1** has been a popular target by both academic and industrial scientists. By application of cycloaddition and cross coupling the native carboxylate required for DA can be employed directly to produce epibatidine **1** in five steps (for optimization and in depth analysis of previous approaches, see SI section E) in 38% gram-scale overall yield (**Figure 3E**). It is worth noting that the key decarboxylative cross coupling takes place in 95% isolated yield (gram-scale, 72% yield). SaphrisTM (asenapine, **102**, **Figure 3F**), an FDA-approved antipsychotic, is currently marketed as a racemic mixture (although the (+)-isomer has superior pharmacokinetic properties)²⁵. This near-symmetric molecule has been challenging to prepare enantioselectively as the two aromatic systems differ only in one chlorine substituent. It is therefore hard to envisage a cycloaddition that could be rendered enantioselective for the preparation of **102**, and only one enantioselective approach has been reported (16 steps)²⁶. In contrast, **102** could be prepared in formally six steps from **B**₂ with complete enantiocontrol by a strategy that could also be used to make an array of near-symmetric analogs. Epothilone, a famous microtubule inhibitor natural product that inspired the FDA-approved medicine Ixabepilone²⁷, has been the subject of numerous synthetic studies and analog campaigns²⁸. Intermediate **105** (**Figure 3G**) was utilized during Nicolaou's synthesis of a cyclobutyl-containing analog and required 15 steps (24% overall yield) to be prepared in enantiopure form starting from **C**₁ *via* enzymatic desymmetrization and a series of carefully choreographed homologations²⁸. Using the same starting material **C**₁ could be prepared in only eight steps through sequential desymmetrization, RCC with alkyne **103**, hydrolysis, RCC with alkyl zinc **104**, protecting group exchange, and finally hydroboration/

oxidation. Differentially substituted norbornene rings have been shown to be useful phenyl bioisosteres in medicinal chemistry however their broad implementation is hindered by a lack of methods for their rapid modular construction (unlike aryl systems)²⁹. In collaboration with LEO Pharma, a key target for an ongoing program (**109**, **Figure 3H**) was prepared from DA adduct **106** via alkene hydration and RCC with the pyrazole-boronic ester **108** in 44% yield. It is worth noting that this is the first report of a RCC reaction using a BPIn derivative rather than a boronic acid. This advance was achieved using an *in situ* prepared ate complex prepared by adding one equivalent of *n*-BuLi relative to the aryl-BPIn donor³⁰. This modification of our Suzuki-RCC protocol was also employed to prepare cyclopropanes **91**, **92** and **93**. Finally, an ongoing program at Eisai necessitated the preparation of complex scaffold **114** (**Figure 3I**) wherein the key SAR to be explored resided at the aryl (green) portion of the molecule. This is a particularly powerful application of the strategy outlined herein since a carboxylate, needed to achieve the diastereoselective DA to construct the decalin framework, served as a gateway for the exploration of chemical space at the desired position. Thus, an asymmetric DA reaction using Corey's oxazaborolidine³¹ catalyst followed by functional group manipulations (See SI section I) led to intermediate **112** which could be cross coupled with boronic acid **113** in a particularly challenging context to deliver **114** and enable biological follow-up.

The strategy outlined here could be useful for more than just forging C–C linkages through cross-coupling. The incorporation of classic nucleophilic (ketone synthesis) and decarboxylative functionalizations (Hunsdiecker reaction, Curtius and Wolff rearrangements) of intermediate adducts opens innumerable possibilities for diversification rendering access to previously inaccessible building blocks (**Figure 3J**). As an example, a chiral 2 π enamine synthon was employed for the preparation of the EED protein–protein inhibitor **118** ($K_i=4$ nM) that was previously prepared by AbbVie³² through a non-modular, racemic [3+2] approach in 1.9% overall yield. In contrast, optically pure **118** (97% ee) was prepared from *meso* scaffold **B2** utilizing RCC followed by Curtius rearrangement in 13% overall yield.

The advance described herein is mainly strategic in nature and thus the underlying limitations are mainly tied to individual parameters of a particular cycloaddition and ensuing RCC reactions. That said, *cis*-1,2-disubstituted products are not currently accessible unless downstream isomerization reactions are pursued which need to be evaluated on a case-by-case basis or decarboxylative non-isomerizing processes are employed (e.g. Curtius). While ligand-controlled RCC reactions might eventually address this issue, in its current form this platform for modular molecular assembly holds great promise for accessing new areas of chemical space. The combination of classic cycloaddition chemistry with newly emerging radical C–C coupling offers a powerful way to repurpose the most classic skeleton-building reactions of organic synthesis to simplify the enantioselective preparation of building blocks, natural products, and medicines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Extended Data

Extended Data Figure 1.

Complete substrate scope of [4+2] cycloaddition/cross-couplings. See Supplementary Information for synthetic details. R¹, R² = (Het)Aryl, alkyl, alkenyl, alkynyl. X-ray structure data is available for compounds 11, 19, 23, 25, 28, 44, 45, 49,

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A Cycloaddition and C–C cross coupling

<p>epibatidine 1</p> <p>Losartan (Cozaar®) 2</p>	Cycloadditions	Concerted/ pericyclic (substrate controlled)	2	Sterics/ electronics	Multiple rings/ complex architecture	Boutique building blocks
		Mechanism	New Bonds Formed	Predictability	Complexity	Starting Material Availability
	$R-X + R'-M$	Transition metal- mediated (ligand controlled)	1	Easily programmed coupling partners	Single C–C bond	Ubiquitous
Combining the best strategic assets of powerful transforms						

B Case study

C Maleic anhydride as chiral dihalide surrogate

Figure 1. Combining the logic of cycloaddition and C–C cross coupling.

A, Cycloaddition and C–C cross coupling; **B**, Case study: retrosynthetic analysis of enantiopure building block **3**; **C**, Maleic anhydride used as available and modular chiral dihalide surrogate.

Figure 2. Substrate scope of combining cycloaddition and C–C cross coupling. A–D

The cycloaddition component is shown in black, the first cross coupling is shown in green and the 2nd cross coupling is shown in blue. The yield and *ee* refer to the 2nd cross coupling. Besides compound **89** (dr 8.5:1), excellent diastereoselectivity (dr >10:1) was observed in all cross couplings. See Extended Data Figures 1 and 2 for complete substrate scope and Supplementary Information for synthetic details. X-ray structure data is available for compounds **11**, **19**, **23**, **25**, **28**, **65** and **C₂**. N = Negishi; S = Suzuki; K = Kumada cross-coupling; N = Boc, *tert*-butoxycarbonyl; TIPS, triisopropylsilyl; Ts, tosyl;

Figure 3. Applications of combining cycloaddition and C–C cross coupling.

A, gram-scale synthesis of (±)-epibatidine. B, asymmetric synthesis of asenapine (Saphris™). C, modular synthesis towards epothilone analogue fragment. D, synthesis of LEO Pharma key intermediate. E, synthesis of Eisai Pharmaceutical key intermediate. F, New chiral 2π synthons for cycloaddition: application to the modular asymmetric synthesis of EED protein-protein interaction inhibitor. Excellent diastereoselectivity (*dr* > 10:1) was observed in all cross couplings. See Supplementary Information for full synthetic details and schemes. X-ray structure data is available for compounds **1**, **107** and **118**. Boc, *tert*-butyloxycarbonyl; Pin, pinacol group; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TCNHPI, tetrachloro-*N*-hydroxyphthalimide; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl.