Modular, stereocontrolled Cβ–H/Cα–C activation of alkyl carboxylic acids

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The union of two powerful transformations, directed C–H activation and decarboxylative cross-coupling, for the enantioselective synthesis of vicinally functionalized alkyl, carbocyclic, and heterocyclic compounds is described. Starting from simple carboxylic acid building blocks, this modular sequence exploits the residual directing group to access more than 50 scaffolds that would be otherwise extremely difficult to prepare. The practical use of these two transformations accomplishes a formal vicinal difunctionalization of carbon centers in a way that is modular and thus, amenable to rapid diversity incorporation. A simplification of routes to known preclinical drug candidates is presented along with the rapid diversification of an antimarial compound series.

C–H activation | decarboxylative cross-coupling | modular | stereocontrolled | carboxylic acids

It is becoming increasingly clear that practitioners are no longer bound by the notion that the pervasive C–H bond is unresponsive to manipulation. In fact, the past two decades have seen a dramatic increase in the use of C–H functionalization logic (1–3) to assemble molecules (4–16). At this juncture, it can be considered part of the mainstream in terms of the way that students learn retrosynthetic analysis (17, 18). One of today’s workhorse C–H activation strategies involves the use of native functional groups to direct and guide the site of functionalization (19–24). As the most ubiquitous functional group in organic chemistry, carboxylic acids and their derivatives have naturally risen to the top in terms of directed C–H functionalization reactions available to the practitioner (Fig. 1A) (25–29). With over 1,000 reports now present for the use of such guided C–H activations (1–3) in synthesis, it is fair to say that this is a staple reaction manifold for modern organic synthesis. In this context, an exploration of serial reactivity in which the lingering carboxylate group is used in successive reactions has been limited in scope. Of the few notable examples, nearly all are restricted to restoration of the parent carboxylic acid followed by classic reactions, such as amidation and esterification (Fig. 1A) (30, 31). The recent development of robust methods to decarboxylate such systems and programmatically replace them with new C–C and C–B bonds in a stereochemically predictable way, a formal type of C–C activation, opens opportunities to leverage the power of carboxylate-directed C–H activation chemistry. This combination of one (32) and two-electron disconnections would enable pathways to potentially valuable chiral acyclic building blocks, such as 3, that could be considered “retrosynthetically opaque,” as it is not immediately apparent how a simple building block, like 3-(3-bromophenyl) propionic acid (4), could be used as its precursor (Fig. 1B) (33). Within the privileged realm of saturated cyclic heterocycles, such logic could be used to rapidly access libraries of enantiopure scaffolds that would be rather difficult to otherwise prepare (Fig. 1C) (34–37). For example, chiral pyrrolidines, such as 5, have previously been prepared through labor-intensive routes that require chiral resolution and are not amenable to late-stage diversity incorporation (38, 39). In stark contrast, a combination of C–H activation and radical cross-coupling strategies (33) could access the same architectures in fewer steps with exquisite control of stereochemistry and allow for diverse arenas to be installed at the end of the route starting from simple commercial carboxylic acids. The difficulty in preparing such seemingly simple molecules is directly related to the challenge of “escaping the flatland” as articulated by many in the field (40, 41). Herein, we present a strategy for the net vicinal difunctionalization of cyclic and acyclic systems via sequential functionalization initiated by stereoselective C–H activation followed by decarboxylative cross-coupling (dCC) to form a variety of C–C and C–X bonds, including aryl (42, 43), alkenyl (44), alkynyl (45), alkyl (26, 46), and boryl (47, 48). The inherent modularity of this strategic advance allows access to a wealth of acyclic and cyclic systems, some of which have been prepared before in more laborious ways. Application to a promising series of heretofore inaccessible azetidine-based antimalarial agents is also disclosed.

Results and Discussion

Proof of Concept. To obtain a first proof of concept for the underlying strategy, a set of enantiopure carboxylic acids, prepared

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Proof of Concept.

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Significance.

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using Pd-catalyzed ligand-enabled asymmetric sp³ C–H activation, was used (Fig. 2) (49–51). Recalling the suite of dCC reactions developed over the last several years (52), the succeeding reaction was found to be tolerant of a variety of pendant functional groups, including esters (19 and 20) and boronic esters (14 and 16), as well as both free (18) and silyl-capped alkynes (15), all of which can be used in yet another reaction sequence on liberation. Importantly, pyridine and boron can be incorporated in the challenging context of strained carbocycles to access trans-disubstituted cyclobutane (23) and cyclopropane (24) rings with high enantiomeric purity, the latter of which could be conducted without a directing group. The ligand-controlled nature of the C–H activation step allows for easily tunable access to either desired enantiomer (i.e., 14 vs. 21) (49–51).

Scope of Saturated Heterocycles. In acknowledgment of the increasing demand for saturated heterocycles in drug development (53, 54), the efficacy of this reaction sequence was demonstrated using an array of commercial heterocyclic acids (both enantiomers of each are available) as shown in Fig. 3. Beyond their importance as a framework for the celebrated β-lactam therapeutic class (55–58), azetidines have garnered recent interest as scaffolds in diversity-oriented synthesis, through which a wide variety of constrained (i.e., bridged or fused) or densely substituted
Fig. 3. Scope of saturated heterocycles. (A) Azetidine core; (B) pyrrolidine core; (C) tetrahydrofuran core; (D) C-2 piperidine core; (E) C-3 piperidine core; (F) morpholine. General conditions for C–H activation reaction (SI Appendix has details): amide (1 eq), Aryl-I (3 eq), Pd(OAc)$_2$ (10 mol %), and AgOAc (2 eq), 110 °C, 38 h. General conditions for directing group removal (SI Appendix has details): arylated amide (1 eq), Boc$_2$O (20 eq), 4-dimethylaminopyridine (DMAP) (3 eq), MeCN (1 M), 70 °C, 12 h. Then, LiOH·H$_2$O (2 eq), 30% H$_2$O$_2$ (5.0 eq), THF:H$_2$O=3:1, 0 °C to room temperature (rt), 18 h. General conditions for dCC reaction (SI Appendix has details): [N] TCNHPI ester (0.1 mmol, 1 eq), zinc reagent (0.2 mmol, 2 eq), NiCl$_2$·glyme (10–50 mol %), di$_2$BuBipy (20–60 mol %), THF:N,N-dimethylformamide (DMF) = 3:2, rt, 12 h. [S] TCNHPI ester (0.1 mmol, 1 eq), boronic acid (0.3 mmol, 3 eq), NiCl$_2$·6H$_2$O (20–50 mol %), Bathophenantroline (22–60 mol %), Et$_3$N (1 mmol, 10 eq), 1,4-dioxiane:DMF = 10:1, 75 °C, 12 h. [G] TCNHPI ester (0.1 mmol, 1 eq), Michael acceptor (0.2 mmol, 2 eq), LiCl, rt, 24 h. [K] TCNHPI ester (0.1 mmol, 1 eq), Grignard reagent (0.15 mmol, 1.5 eq), FeBr$_3$·H$_2$O (20 mol %), NMP, −15 °C, 15 min. *No ee reported for this example, as racemic compound was not prepared. DG, directing group.
nitrogenous ring systems can be accessed (59). To this point, arylated intermediates derived from N-protected azetidine-2-carboxylic acid (Fig. 3A) can be rapidly diversified under the Suzuki (29–32), Negishi (28), and Giese (26 and 27) protocols. In a similar vein, elaboration of Cbz-protected proline via directed C–H arylation at C3 followed by dCC furnished a range of enantiopure trans-1,2-difunctionalized pyrrolidines bearing diverse substituents, such as aryl (35 and 39), heteroaryl (36–38 and 40), cycloalkyl (33), and alkenyl (34) functionalities (Fig. 3B). Substrate 45 is of particular note, as prior routes to access one of the rare forms of pipecolic acid. When 3,4-difunctionalized pyrrolidines bearing di- or trisubstituents, such as aryl (54), heteroaryl (57 and 59), and alkenyl (53) moieties at C2. All of these structures are new chemical entities despite their simplicity—even distant relatives are rare. It is difficult to conceive of a more direct and modular approach to such scaffolds with either enantiomeric form available simply by choosing t or d forms of pyrrolidine. When 3,4-piperidine substitution is desired, N-Boc-piperidine-3-carboxylic acid (Fig. 3F) may be used (60–65), as the given C–H activation takes place selectively at C–4 vs. C–2. Given the structural similarity to the blockbuster drug Paxil (paroxetine), rapid access to such systems is noteworthy. Finally, the logic outlined above can be applied to substituted morpholines (53, 54)—one of the rare saturated, bis-heteroatom–containing systems to top frequency lists in Food and Drug Administration approvals—as detailed in Fig. 3F. Although the C–H activation step is limited to methoxylolation at this juncture (SI Appendix discusses attempted C–H arylation and methylation), it does represent an example of C–H activation of such heterocycle.

Synthesis of Hit-to-Lead Candidates and Late-Stage Intermediates. In addition to the diverse scope outlined above, the described reaction series was next evaluated for its capacity to simplify the synthesis of active hit-to-lead series and late-stage intermediates (Fig. 4). Of particular note in these case studies is how the logic presented herein can be used as both a means to effectively access a specific target or a library of similar structures simply by changing coupling partners. Monoamine transporter ligand 69 is a vivid demonstration of this (61, 62). The first synthesis of this molecule utilized conjugate addition to arecoline 70 followed by a series of functional group manipulations to arrive at 69 in 8.6% overall yield after chiral resolution (63). Use of the current vicinal difunctionalization strategy deleted many of those concession steps and could be used to access 69 (11.2% overall yield; >20:1 diastereomeric ratio; 97% enantiomeric excess) and in principle, a whole library of enantiopure analogs in only six steps. The leukotriene B4 inhibitor BIRZ-227 (Fig. 4B) (71), a trans-diarylpyrrolidine, is another prime example of how customary logic falters if a diverse, modularly assembled library is targeted. Indeed, the sole reported preparative-scale protocol to its precursor 5 opts for a pyrrolidine core construction in the initial step, placing severe limitations for rapid diversification (37, 38). To access enantiopure intermediates, an enzyme-assisted resolution is required, which itself requires multiple extraneous steps. Instead, the sequential C–H arylation/dCC approach begins from an inexpensive enantiopure amino acid building block (Pro), which is subjected to standard directing group installation, followed by C–H arylation/hydrolysis and the desired dCC to arrive at diarylated compound 5. Should further diversification be of interest, any number of analogs may be forged in short order, with no resolution necessary.

Structural Diversification of Azetidines with in Vitro Antimalarial Activity. We finally applied the sequential functionalization tactic to the design and synthesis of azetidine-containing small molecules that potently inhibit the asexual blood stages of Plasmodium parasites. Plasmodium infections continue to cause over 200 million clinical cases of malaria each year, leading to an estimated 435,000 deaths in 2017 (64). Emerging resistance to frontline drugs, an issue currently curbed by means of combination therapies (64, 65).

**Fig. 4.** Synthesis of hit-to-lead candidates and late-stage intermediates. (A) Synthesis of monoamine transporter ligand (69); (B) modular synthesis of LTB4 inhibitor, BIRZ-227 (71). DG, directing group.
underscores the need for antimalarials that act via novel mechanisms of action (nMoA). Recently, Kato et al. (66) reported the discovery of potent nMoA antimalarials enabled by phenotypic high-throughput screening (see Malaria Therapeutics Response Portal, https://portals.broadinstitute.org/mtrp). An unpursued promising hit from the same screening campaign is the tri-substituted azetidine BRD8468 (72; Malaria Therapeutics Response Portal) (Fig. 5A) (Malaria Therapeutics Response Portal). Importantly, BRD8468 may inhibit parasite growth via nMoA, because it remains equipotent against a panel of

![Fig. 5.](https://portals.broadinstitute.org/mtrp)

Fig. 5. Structural diversification of azetidines with in vitro antimalarial activity. (A) Analogs of phenotypic screening hit BRD8488 (72): approach; (B) analog synthesis and biological evaluation; (C) analog 80 inhibits growth of wild-type and drug-resistant Pf strains in vitro with similar potencies. DG, directing group.
drug-resistant lines that have been used to identify compounds acting through known mechanisms of action, such as inhibitors of *Plasmodium falciparum* (Pf) ATP4, PfP4K, and various targets in the mitochondrial electron transport chain, like PfDHODH (SI Appendix) (Pf is the deadliest species of *Plasmodium* that causes malaria in humans). Also of note, Cε-epimer BRD5530 showed significantly lower potency than BRD8468 (up to 25-fold) (SI Appendix), indicating in turn that the trans-relationship between the biaryl substituent and the vicinal alkylic group is critical for activity. In this context, we envisioned a structural simplification of BRD8468 consisting of the removal of the hydroxymethyl group at C6. If successful (i.e., conducive to potent analogs), this strategy would enable both (i) significant abbreviation of synthetic routes, rendering the chemical series more attractive in terms of developability [guidelines on antimalarial development, including recom-}
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