

Direct Catalytic Enantioselective Benzoylation from Aryl Acetic Acids

Patrick J. Moon,[†] Zhongyu Wei,[†] and Rylan J. Lundgren*[‡]

Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

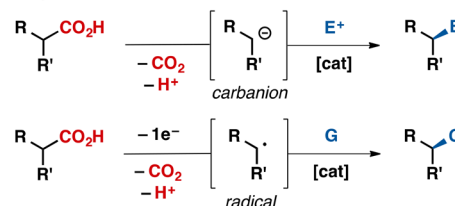
S Supporting Information

ABSTRACT: We demonstrate that metal-catalyzed enantioselective benzoylation reactions of allylic electrophiles can occur directly from aryl acetic acids. The reaction proceeds via a pathway in which decarboxylation is the terminal event, occurring after stereoselective carbon–carbon bond formation. This mechanistic feature enables enantioselective benzoylation without the generation of a highly basic nucleophile. Thus, the process has broad functional group compatibility that would not be possible employing established protocols.

Carboxylic acids are stable and abundant chemical feedstocks, making them ideal starting materials in chemical synthesis.¹ The extrusion of CO₂ from organic acids and their derivatives is a key mechanistic step in both classical and emerging bond-forming methodologies used in the preparation of functional molecules.² Unmodified carboxylic acids are typically directly engaged in catalytic enantioselective processes through mechanistic pathways initiated by decarboxylation to generate a reactive intermediate. Ionic decarboxylation leads to a carbanion intermediate that can be intercepted stereoselectively with electrophiles (Figure 1a).³ Alternatively, single electron oxidation leads to the loss of CO₂ by homolysis, generation of a radical species, and stereoselective trapping with a chiral catalyst and a suitable reaction partner (Figure 1a).⁴ In both these reaction manifolds, acid substrates that are otherwise recalcitrant toward decarboxylation can be covalently modified by fragments that can undergo oxidative insertion^{2,5} or those that induce homolysis⁶ in order to initiate reactivity. These indirect acid coupling strategies decrease overall process economy and efficiency.

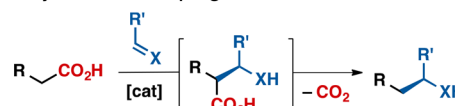
A third mechanistic framework involves a stereoselective bond-forming event prior to decarboxylation (Figure 1b).⁷ As the selectivity-determining bond forming event is separate from the decarboxylation step, this pathway has potential advantage over methods relying upon the irreversible generation and trapping of reactive intermediates. Functionality that would quench highly nucleophilic species (protic groups, electrophiles) or intercept radicals (π -systems, weak abstractable CH bonds) could be tolerated in this pathway, providing broad chemoselectivity and functional group compatibility, which are hallmarks of enabling synthetic methodologies.⁸ The ability to induce an enantioselective metal-catalyzed cross-coupling event adjacent to a free carboxylate unit without irreversible interference from the acid itself, however, presents a major difficulty. Efforts to exploit this type of reactivity have been restricted to the use of

A Decarboxylation Generates Reactive Intermediate



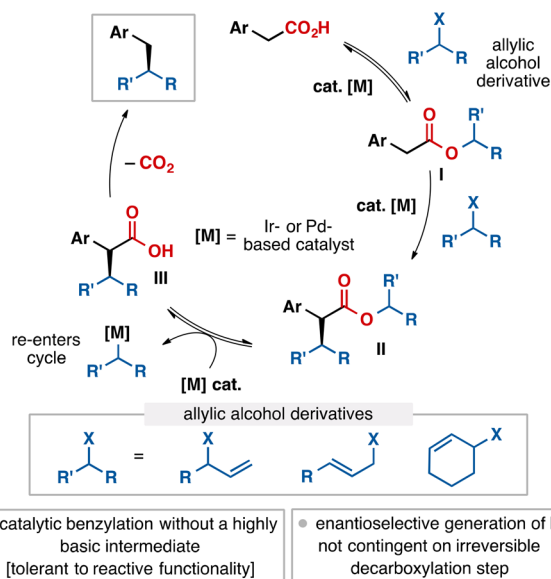
- stereoselective trapping of reactive intermediate [challenging]
- electrophiles, R[•] acceptors quench intermediate [chemoselectivity problem]

B Decarboxylation Post Coupling Event



- selectivity-determining step prior to decarboxylation [improved compatibility]
- limited to addition reactions to polarized π -units [Aldol, Mannich]

C Potential Mechanism for Decarboxylative Benzoylation



- catalytic benzoylation without a highly basic intermediate [tolerant to reactive functionality]
- enantioselective generation of II not contingent on irreversible decarboxylation step

Figure 1. Mechanisms for enantioselective decarboxylative reactions. (A) Ionic or radical paths. (B) Decarboxylation after stereo-determining step. (C) Mechanistic hypothesis for an enantioselective benzoylation process from aryl acetic acids.

malonic half esters and related α -carboxy carbonyl substrates in aldol reactions and related additions to π -electrophiles,^{2a,7,9}

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thus their larger potential in selective synthesis remains unrealized.

In considering new transformations that could leverage the advantage of predecarboxylative coupling of acids in enantioselective catalysis, we questioned whether aryl acetic acids¹⁰ could be used as benzylating reagents in metal-catalyzed asymmetric coupling reactions. In particular, we sought to develop the stereocontrolled benzylation of allylic electrophiles,^{11,12} owing to the diverse utility of chiral allylated products and the known ability of transition metals to affect nucleophile allylation processes.¹³ This approach would contrast methods that require stoichiometric quantities of strong base to generate highly reactive benzyl anions from 2-pyridinyl substrates¹⁴ or Cr(CO)₃ complexed toluenes.¹⁵

A pathway for the decarboxylative benzylation could involve reversible metal-catalyzed carboxylate O-allylation from an allylic electrophile to generate an allyl aryl acetate (I in Figure 1c). This species could undergo a second metal-catalyzed allylic substitution at the enolate position to form a new carbon–carbon bond (II). Reversible O-deallylation via oxidative insertion would generate a new metal-allyl fragment for re-entry into the catalytic cycle and liberate the functionalized carboxylic acid (III). At this stage, the decarboxylation event would generate the benzylated C(sp³)–C(sp³) coupled product. As the key stereocenter is generated prior to decarboxylation, substrates less prone to CO₂ extrusion could be subjected to reaction conditions to enable product formation without impacting the selectivity determining step (ie by heating). This strategy would allow for enantioselective benzylation to occur without the generation of a strongly basic, functional group-intolerant benzyl anion, enabling the reaction to occur in the presence of protic and electrophilic groups.¹⁶ Furthermore, the process has the potential to be highly chemoselective for benzylic acids in the presence of other carboxylic acid groups typically employed in radical- or ionic-decarboxylative cross-coupling reactions, should O-allylation be reversible over the course of the reaction.^{17,18}

Figure 2a provides an example of the enantioselective decarboxylative benzylation of allylic electrophiles. In the presence of Ir-catalyst [Ir]-1¹⁹ and DBU, the diacid substrate (1) undergoes enantioselective coupling exclusively at the benzylic position to generate 2a without interference from the benzoic acid unit. Monitoring of reaction mixtures using a series of simpler aryl acetic acids clearly showed the rapid generation and slow decay of intermediate I, which converts to II that is formed as an ultimately inconsequential mixture of diastereomers with high enantioselectivity at the allylic position. Species II readily O-deallylates to form III, which decarboxylates to give the chiral benzylated product. These observations, along with crossover experiments, confirmed the mechanistic hypothesis outlined in Figure 1c (see Figures S1 and S2 in the SI for details). The generality of the approach is demonstrated with the benzylation of cyclic allylic electrophiles (3a) via Pd-catalysis using a Trost-type system²⁰ and BSA as the base (Figure 2b). In cases where decarboxylation is not spontaneous at room temperature, heating the reaction at 70–90 °C for short periods of time delivers product with high yield and no impact on enantioselectivity (2b–2g, Figure 2c).

A comprehensive functional group compatibility survey showed the reaction proceeded with similar yields and enantioselectivities in the presence of electrophilic and protic groups (aldehyde, ketone, free NH-groups, alkyl chloride, N-Boc amino acid, alkyl alcohol, phenol, alternative carboxylic

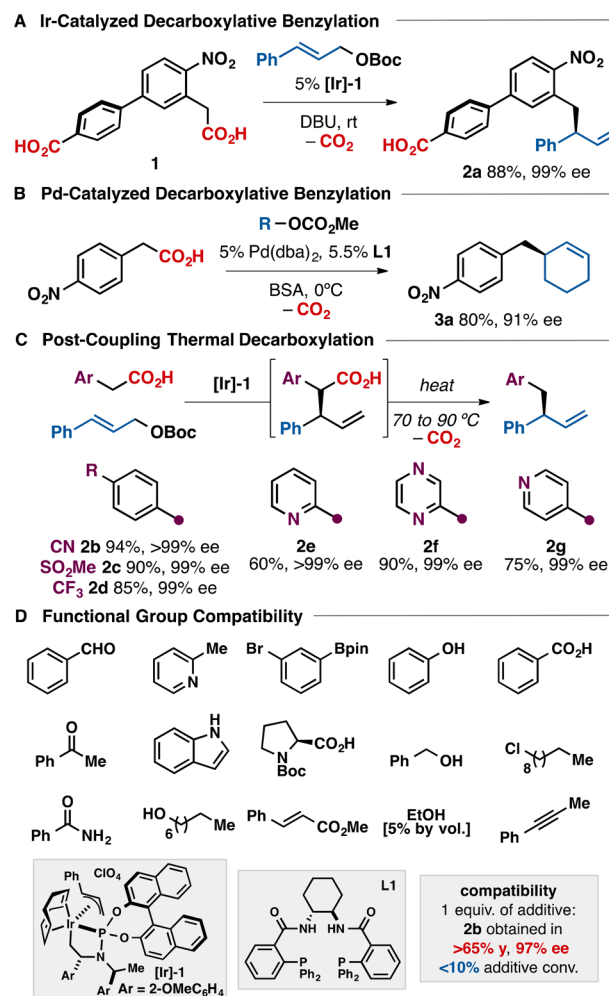


Figure 2. (A) Ir-catalyzed process. (B) Pd-catalyzed process. (C) Postcoupling decarboxylation. (D) Examples of functional group compatibility. Yields determined by ¹H NMR, see SI for details.

acids, conjugate acceptors, N-heterocycles Figure 2d, see Figures S3–S5 for more examples). Many of these groups would quench or undergo other reactions with organometallic nucleophiles, or species generated upon single-electron oxidation, highlighting the advantage of the current approach.

The scope of the enantioselective benzylation is demonstrated in Figure 3.²¹ A combination of aryl acetic acid and allylic carbonate or allyl aryl acetate esters can be used as substrate components. The alcohol activation step (carbonate vs ester) differentiates these methods and provides additional flexibility in substrate preparation. In the case of Ir-catalyzed reactions, uniformly high enantioselectivities (97–99% ee) are observed across a range of benzyl partners, including N-heterocycles (2e, 2f, 2g), substrates bearing potentially reactive electrophilic or protic functionality (2i, 2j, 2k, 2n, 2r, 2s, 2t) including aryl iodides, aldehydes, other carboxylic acid groups, and polysubstituted reagents (2n, 2r, 2s, 2u, 2v). Catalyst loadings as low as 0.1 mol % can be employed in some cases. Products derived from aryl acetic acid substrates that are resistant to decarboxylative coupling under the standard conditions can be easily accessed in reasonable yield by nitro group manipulations (52–86% yield, 97–99% ee 2w, 2x, 2y). The allyl fragment can vary in structure and also host a number of potentially reactive functional groups without significant change to process efficiency (halogens, NH-groups, N- and S-

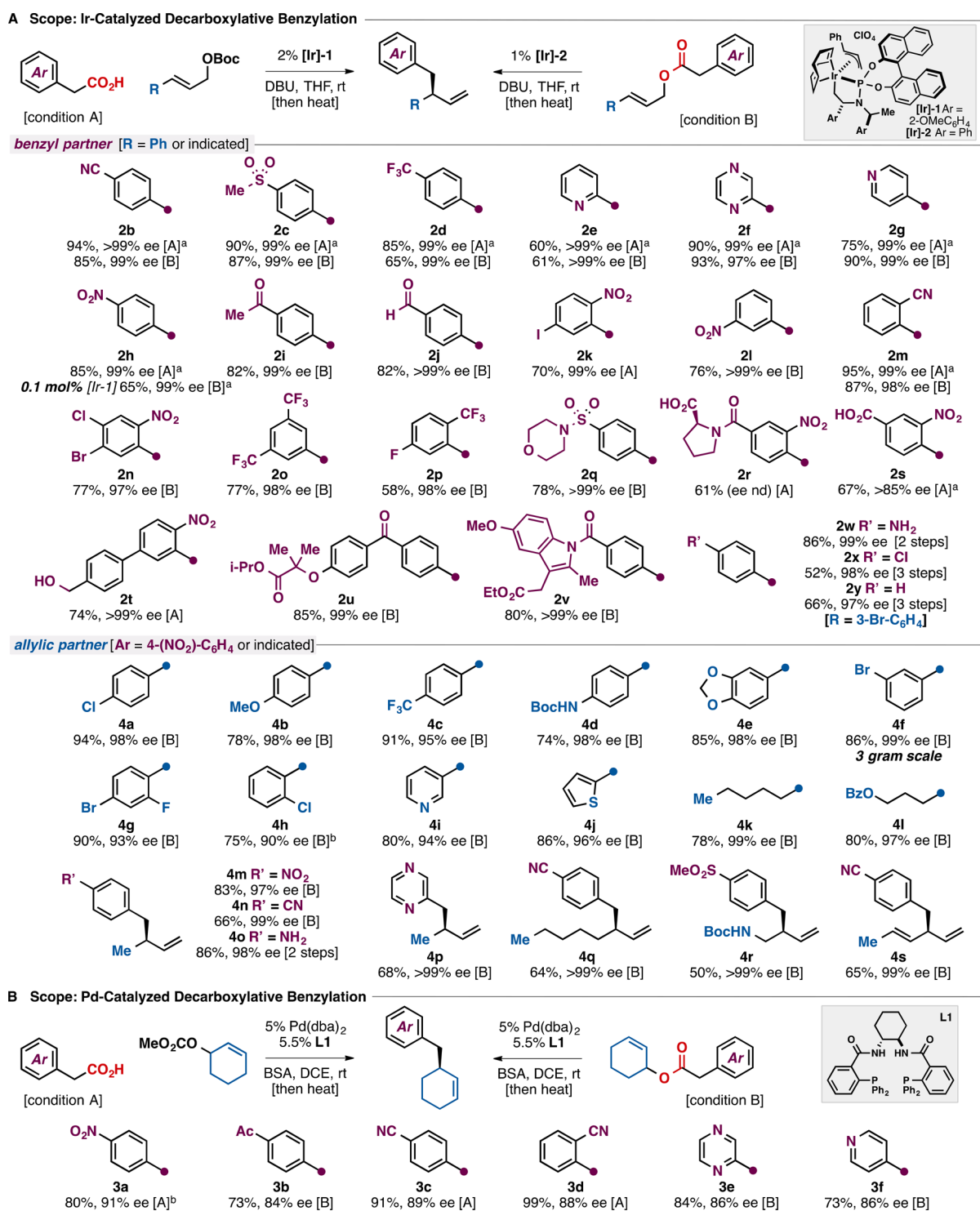


Figure 3. Scope of the enantioselective decarboxylative benzylation (A) Ir-catalyzed process. (B) Pd-catalyzed process. Unless noted, yields are of isolated material. See SI for complete details. ^aYield determined by ¹H NMR using an internal standard; ^bconducted at 0 °C.

heterocycles, 90–99% ee). Alkyl-substituted allylic electrophiles are competent partners, giving access to simple methyl (4m–4p), long-chain alkyl (4k, 4q), and heteroatom-substituted (4l, 4r) chiral benzylated products.²² Pd-catalyzed processes can be used to access benzylated cyclic allylic stereocenters with slightly lower selectivity (83–91% ee), but similarly broad scope of aryl acetic acid partner from either allylic carbonates or allylic ester electrophiles (3a–3f).

The use of this method to access high-value, chiral benzylated intermediates of importance to human health was demonstrated by the expedient preparation of the core fragments of Elacestrant and Taranabant (Figure 4). Briefly, condensation between aryl acetic acids and suitably functionalized allylic alcohols, followed by Ir-catalyzed enantioselective decarboxylative benzylation gives effectively single-enantiomer products (5a, 4f both 99% ee) primed for conversion to bioactive targets, including at multigram scale. Ring-closing

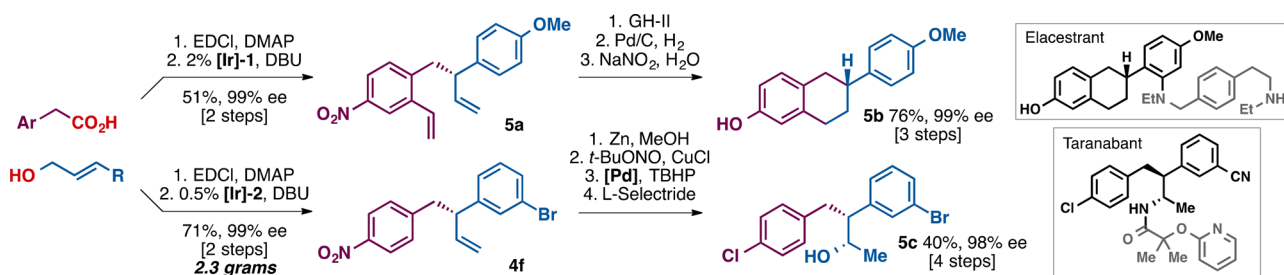


Figure 4. Applications: Synthesis of the cyclic core of Elacestrant and a late-stage intermediate of Taranabant, see the SI for details.

metathesis, hydrogenation, and Sandmeyer hydroxylation convert **5a** to cyclic product **5b**, which bears the chiral core of Elacestrant.²³ Conversion of the nitro group in **4f** to chlorine, followed by ketone-selective Wacker oxidation²⁴ and diastereoselective reduction gives product **5c**, which can be converted to (*ent*)-Taranabant via an established route.²⁵

The enantioselective benzylation of allylic electrophiles, directly from aryl acetic acids has been established. The reaction proceeds via a pathway in which decarboxylation is the terminal event, occurring after stereoselective carbon–carbon bond formation, enabling the tolerance of protic and electrophilic functionality. Collectively, these studies show this approach has value in generating carbon–carbon bonds with high levels of enantioselectivity in the presence of complex chemical functionality.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11390.

Experimental procedures and compound characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

*rylan.lundgren@ualberta.ca

ORCID

Rylan J. Lundgren: 0000-0002-7760-6946

Author Contributions

[†]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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