Catalytic Enantioselective Benzylation Directly from Aryl Acetic Acids

Patrick J. Moon*, Zhongyu Wei*, Rylan J. Lundgren†

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

*These authors contributed equally to this work
†Corresponding author. Email: rylan.lundgren@ualberta.ca

Abstract: The stability and wide availability of carboxylic acids make them valuable reagents in chemical synthesis. Most transition metal catalyzed processes using carboxylic acid substrates are initiated by a decarboxylation event that generates reactive carbanion or radical intermediates. Developing enantioselective methodologies relying on these principles can be challenging, as highly reactive species tend to react indiscriminately without selectivity. Furthermore, anionic or radical intermediates generated from decarboxylation can be incompatible with protic and electrophilic functionality, or groups that undergo trapping with radicals. We demonstrate that metal-catalyzed enantioselective benzylation 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. The mechanistic features of the process enable enantioselective benzylation 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 which can be intercepted stereoselectively with electrophiles (Fig. 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 (Fig. 1a).⁴ In both these reaction manifolds, acid substrates that are otherwise recalcitrant towards decarboxylation can be covalently modified by fragments that can undergo oxidative insertion²b,⁵ or those
Fig 1. Mechanistic pathways for catalytic, enantioselective reactions of carboxylic acids. (A) Ionic or radical decarboxylation as the primary event. (B) Decarboxylation after stereodetermining step. (C) Mechanistic hypothesis for the development of a metal-catalyzed enantioselective benzylation process from aryl acetic acids and its potential advantages.

that induce homolysis 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 (Fig. 1b). As the selectivity-determining bond forming event is separate from the decarboxylation step, this pathway has distinct 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 – hallmarks of enabling synthetic methodologies. 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 malonic half esters and related β-carboxy carbonyl substrates in aldol reactions and additions to π-electrophiles, thus their larger potential in selective synthesis remains unrealized.

In considering new transformations that could leverage the advantage of pre-decarboxylative coupling of acids in enantioselective catalysis, we questioned whether aryl acetic acids could be used as benzylation reagents in metal-catalyzed asymmetric coupling reactions. In particular, we sought to develop
the stereocontrolled benzylation of allylic electrophiles, owing to the diverse utility of chiral allylated products and the known ability of transition metals to affect nucleophile allylation processes. This approach would contrast methods that require stoichiometric quantities of strong base to generate highly reactive benzyl anions from 2-pyridinyl substrates\textsuperscript{11} or Cr(CO)\textsubscript{3} complexed toluenes.\textsuperscript{12} A feasible pathway for the decarboxylative benzylation would involve reversible metal-catalyzed carboxylate O-allylation from an allylic electrophile to generate an allyl aryl acetate (I in Fig. 1c). The ester species could then undergo a second metal-catalyzed allylic substitution at the enolate position to form a new carbon–carbon bond (II). Catalytic and 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 CO\textsubscript{2} extrusion could be subjected to reaction conditions to enable product formation without impacting the selectivity determining step. Heating the reaction mixture would be the simplest approach. 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. 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. Buoying our hope for a highly enantioselective process were recent reports that aryl acetic esters similar in structure to proposed intermediate I are suitable nucleophiles in metal-catalyzed enantioselective allylic alkylations.\textsuperscript{13} During our studies, Kanai and co-workers demonstrated that allylic esters can undergo Pd/B dual catalyzed fragmentation and recombination to generate chiral homoallylic carboxylic acids (analogous to the conversion of I to III with linear allylic substitution).\textsuperscript{14}

Fig. 2a provides an example of the enantioselective decarboxylative benzylation of allylic electrophiles. In the presence of Ir-catalyst (Ir-1)\textsuperscript{15} and DBU, the diacid substrate (I) undergoes enantioselective coupling exclusively at the benzylic position to generate 2a without inference from the benzoic acid unit (supporting information for optimization details). 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 benzylic position. Species II readily O-deallylates to form III which decarboxylates
Fig 2. Metal-catalyzed enantioselective decarboxylative benzylolation of allylic electrophiles (A) Ir-catalyzed process (B) Pd-catalyzed process (C) Post-coupling decarboxylation (D) Examples of functional group compatibility via intermolecular tolerance screen. Yields determined by $^1$H NMR using an internal standard (see Fig 3 for isolated yields). Enantiomeric excess (ee) determined by HPLC. See supporting information for complete details and additional functional group compatibility data. DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene; BSA = bis(trimethylsilyl)acetamide.

to give the chiral benzylated product. These observations, along with cross-over experiments, confirmed the mechanistic hypothesis outlined in Fig 1c (see Fig S1-S2 the supporting information for details). The generality of the approach is demonstrated with the benzylolation of cyclic allylic electrophiles (3a) via Pd-catalysis using a Trost-type system and BSA as the base (Fig. 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, Fig. 2c). A comprehensive intermolecular functional group compatibility survey showed the reaction proceeded with similar yields and enantioselectivities in the presence of both electrophilic and protic groups (aldehyde, ketone, free NH-groups, alkyl chloride, N-Boc amino acid, alkyl alcohol, phenol, alternative carboxylic acids, conjugate acceptors, N-heterocycles Fig. 2d, see Figs S3–S5 for additional examples and limitations). The majority of
these groups would quench or undergo other reactions with organometallic benzyl nucleophiles, or species generated upon single-electron oxidation conditions, highlighting the advantage of the current approach.

The scope of the enantioselective benzylation is demonstrated in Fig 3. Either 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 overall yields and excellent enantioselectivities by way of simple 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-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. 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 utility of this reaction concept 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 (Fig 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 metathesis, hydrogenation, and Sandmeyer hydroxylation converts 5a to cyclic product 5b which bears the chiral core of Elacestrant.17 Conversion of the nitro group in 4f to chlorine, followed by ketone-selective Wacker oxidation18 and diasteroselective reduction gives product 5c, which can be converted to (ent)-Taranabant via an established route.19 Collectively, these studies show that the use of carboxylic acids as reagents in metal-catalyzed coupling reactions in which decarboxylation occurs as a terminating step has value in generating carbon–carbon bonds with high levels of enantio- and chemoselectivity.
**A  Scope: Ir-Catalyzed Decarboxylative Benzylacylation**

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<td>85%</td>
<td>65%, 99% ee [B]</td>
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<td>2f</td>
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**B  Scope: Pd-Catalyzed Decarboxylative Benzylacylation**

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<td>85%, 86% ee [B]</td>
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<tr>
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<td>73%, 86% ee [B]</td>
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**Fig 3. Scope of the metal-catalyzed enantioselective decarboxylative benzylacylation (A) Ir-catalyzed process (B) Pd-catalyzed process** Unless notes, yields are of isolated material. See supporting information for complete details. aYields determined by 1H NMR using an internal standard. bConducted at 0°C
Fig 4. Applications (A) Synthesis of the cyclic core of Elacestrant. (B) Synthesis of a late-stage intermediate of Taranabant. See supporting information for complete details.

REFERENCES AND NOTES


10.  2000 (hetero)aryl acetic acids are available for purchase via eMolecules, MilliporeSigma lists >1000 compounds with this motif.


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The supporting information section provides details on synthetic procedures, product characterization, Figures S1-S7, HPLC traces and NMR spectra.