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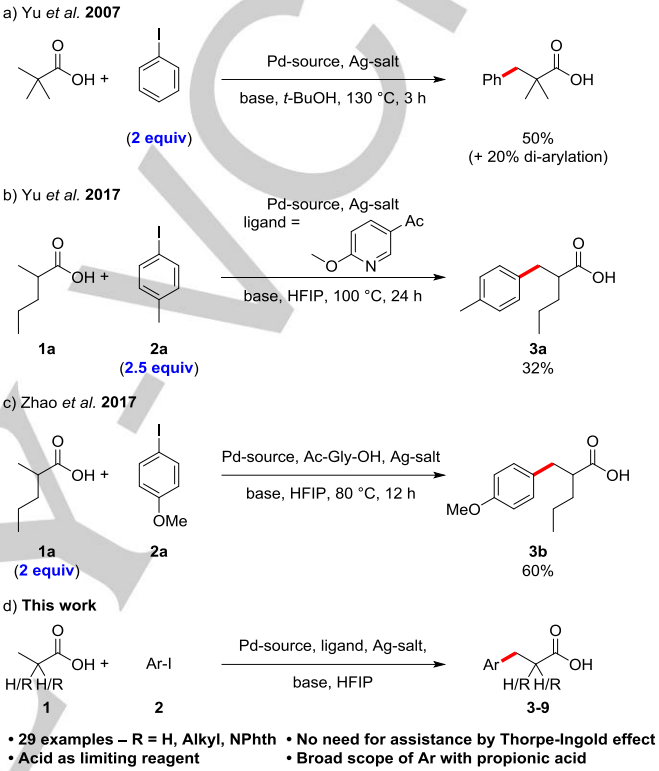
Pd-Catalyzed β-C(sp³)–H Arylation of Propionic Acid and Related Aliphatic Acids

Kiron K. Ghosh,[a] and Manuel van Gemmeren*[a],[b]

Abstract: A generally applicable Pd-catalyzed protocol for the β-C(sp³)–H arylation of propionic acid and related α-branched aliphatic acids is reported. Enabled by the use of *N*-acetyl-β-alanine as ligand our protocol delivers a broad range of arylation products. Notably, the highly challenging substrate, propionic acid, which lacks any acceleration through the Thorpe-Ingold effect, can be employed as substrate with synthetically useful yields. Furthermore, the scalability and synthetic applicability of the protocol are demonstrated.

The carboxylic acid moiety is one of the most elementary and widespread functional groups in organic chemistry. Its importance is reflected by the presence of both carboxylic acids and their derivatives in a variety of natural products and pharmacologically relevant compounds, as well as the plethora of synthetic methods that have been developed for their synthesis and further functionalization.[1] In light of their importance it is not surprising that substantial efforts have been directed towards the use of these compounds as substrates in C–H activation reactions. While carboxylic acids could be utilized with great success as directing groups in C(sp²)–H activation reactions,[2] the corresponding activation of C(sp³)–H bonds of such weakly directing carboxylic acid substrates has remained highly challenging. In order to make use of aliphatic carboxylic acids as substrates, they typically have to be derivatized into suitable directing groups.[3] The drawbacks associated with the need to introduce and remove the directing group render methods directly employing the unmodified carboxylic acid inherently more desirable.

Following early studies on Pt-catalyzed C–H oxidation reactions,[4] the group of Yu reported a Pd-catalyzed C(sp³)–H arylation of pivalic acid and similar α-quaternary substrates in 2007 (Scheme 1a).[5] It should be noted that substrates devoid of α-quaternary centers have proven highly challenging in this type of transformation,[3d] presumably due to the absence of an accelerating Thorpe–Ingold effect.[6] Recently, the same group reported a 32% yield of acid **3a** from the arylation of 2-methylvaleric acid (**1a**) with 4-iodotoluene (**2a**) as part of a study focusing on the ligand enabled C(sp³)–H arylation of N-phthaloyl alanine and analogous compounds using pyridine-derived ligands



Scheme 1. Key studies towards the direct C-H arylation of aliphatic carboxylic acids. Ac = acetyl, HFIP = 1,1,1,3,3,3-hexafluoro-*iso*-propanol, Gly = glycine.

(Scheme 1b).[7] The group of Zhao developed a catalytic system relying on *N*-acetylglycine as a ligand, which delivered comparable results with *N*-phthaloyl alanine as a substrate. Using this catalytic system, the authors also obtained promising results with aliphatic carboxylic acids. For example acid **3b** was synthesized from 4-methoxyiodobenzene (**2b**). It should be noted, however, that the carboxylic acid reaction partner **1a** was employed in excess to achieve the reported yield relative to the aryl iodide as the limiting reagent (Scheme 1c).[8] Despite the substantial advances reported in the studies described above, current methodologies for the arylation of simple aliphatic acids have remained limited in terms of yields and/or the requirement to use an excess of the carboxylic acid substrate. In parallel to these studies, we directed our research specifically towards the β-C(sp³)–H arylation of otherwise unfunctionalized carboxylic acid substrates such as 2-methylvaleric acid (**1a**) or propionic acid (**1b**), which would give access to hydrocinnamic acid derivatives, a structural motif found in a variety of natural products and medicinally relevant compounds (Scheme 1d).[1c] Herein we report the development of a catalytic system for the Pd-catalyzed

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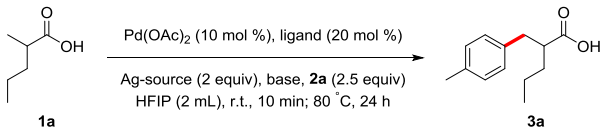
β-C(sp^3)–H arylation of propionic acid and its derivatives. We initiated our studies using 2-methylvaleric acid (**1a**) as a model substrate and 4-iodotoluene (**2a**) as arylating agent (Table 1).[9]

Table 1. Selected examples from the optimization of the reaction conditions for the Pd-catalyzed β-C(sp^3)–H arylation of carboxylic acids.

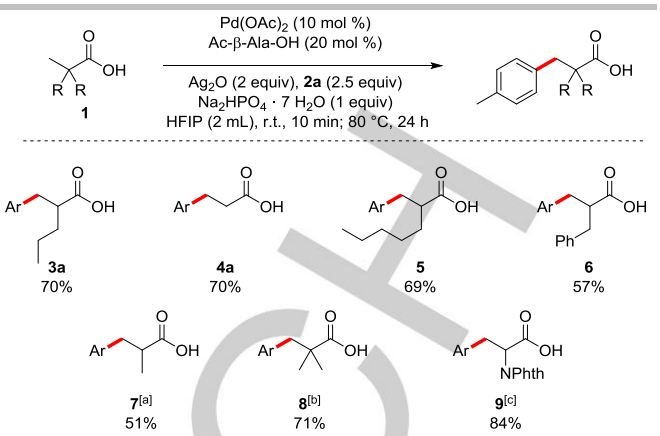


Entry	Ligand	Ag-source	Base	NMR-Yield[a]
1[b]	none	AgOAc	$Na_2HPO_4 \cdot 7\ H_2O$ (1.5 equiv)	22%
2[b]	Ac-Gly-OH	AgOAc	$Na_2HPO_4 \cdot 7\ H_2O$ (1.5 equiv)	39%
3	Ac-Gly-OH	AgOAc	$Na_2HPO_4 \cdot 7\ H_2O$ (1.5 equiv)	44%
4	Ac-Gly-OH	AgOAc	$Na_2HPO_4 \cdot 7\ H_2O$ (1 equiv)	49%
5	Ac-Gly-OH	Ag_2O	$Na_2HPO_4 \cdot 7\ H_2O$ (1 equiv)	56%
6	Ac-Phe-OH	Ag_2O	$Na_2HPO_4 \cdot 7\ H_2O$ (1 equiv)	60%
7	Ac-β-Ala-OH	Ag_2O	$Na_2HPO_4 \cdot 7\ H_2O$ (1 equiv)	68% (70%)
8	Ac-β-Ala-OH	none	$Na_2HPO_4 \cdot 7\ H_2O$ (1 equiv)	9%
9	Ac-β-Ala-OH	Ag_2O	None	24%
10[c]	Ac-β-Ala-OH	Ag_2O	$Na_2HPO_4 \cdot 7\ H_2O$ (1 equiv)	0%

[a] Reactions were conducted on a 0.2 mmol scale. Yields were determined by ^{1}H-NMR spectroscopic analysis of the crude reaction mixture using CH_2Br_2 as internal standard. Isolated yields are given in parentheses. [b] These reactions were conducted at 100 °C. [c] No $Pd(OAc)_2$ was added. Phe = L-phenylalanine, β-Ala = β-alanine.

We were surprised to find that, contrary to the results reported for *N*-phthaloyl alanine,[7] a modest degree of product formation occurred even in the absence of an additional ligand (Entry 1). In fact, a substantial number of prospective ligands tested had a detrimental effect on the formation of acid **3a**.[9] We identified *N*-acetyl glycine as a first promising ligand (Entry 2). Improved results were obtained upon lowering the reaction temperature to 80 °C (Entry 3). Subsequently, we discovered that a reduced amount of base (Entry 4) and the use of silver oxide as a silver-source (Entry 5) further increased the yield. Having identified the otherwise best reaction conditions, we returned our attention to the ligand. After some experimentation we discovered a beneficial effect exerted by ligands leading to a 6- rather than 5-membered ring chelation of the Pd-catalyst,[10] and obtained good yields of acid **3a** using *N*-acetyl-β-alanine as ligand (Entries 6 and 7). Final control experiments confirmed the necessity of all reaction components for the success of the reaction (Entries 8–10).

With suitable reaction conditions in hand, we proceeded to explore the scope of this transformation and began by varying the carboxylic acid component (Scheme 2). The product of our model reaction **3a** was obtained in 70% yield. Encouraged by this finding, we applied our reaction conditions to the even more challenging propionic acid (**1b**) as substrate.[8] We were delighted to find that this substrate could be converted with equal efficiency under our reaction conditions and the hydrocinnamic acid derivative **4a** was



Scheme 2. Scope of the direct β-C(sp^3)–H arylation with respect to the aliphatic carboxylic acids. Unless noted otherwise the reactions were conducted on a 0.2 mmol scale. Phth = Phthaloyl protecting group. [a] The aryl iodide was used as the limiting reagent with 2.5 equivalents of isobutyric acid. [b] The aryl iodide was used as the limiting reagent with 6 equivalents of pivalic acid. [c] Using AgOAc as Ag-source.

obtained in 70% yield. We proceeded to investigate the influence of varied substituents in the α-position of the acid substrate and could obtain the *n*-pentyl- and benzyl-substituted products **5** and **6** in 69% and 57% yield respectively. By modifying the stoichiometry and utilizing the aryl iodide as the limiting reagent the mono-substituted products of both isobutyric acid (**7**, 51%) and pivalic acid (**8**, 71%) could be obtained selectively. Finally, we could demonstrate that *N*-phthaloyl alanine can also be arylated by slightly modifying our reaction conditions and the corresponding product **9** was obtained in 84% yield.

In light of the suitability of our catalytic system for propionic acid (**1b**), we became interested in exploring the scope of aryl iodides with this substrate (Scheme 3a).[11]

We began by studying the influence of substitution patterns of the aryl iodide on the outcome of the reaction. The products derived from unsubstituted iodobenzene (**4c**, 83%), the para-substituted analogs **4d** (75%) and **4e** (71%) and the 3,5-disubstituted **4f** (76%) could all be obtained with similar efficiency.[12] Electron donating substituents on the aryl iodide were likewise well tolerated (**4b**, **4g–i**). Next, the influence of halide substituents on the aryl iodide was probed. The fluorine-substituted **4j**, chlorine-substituted **4k**, and bromine-substituted **5l** products were obtained in 68%, 78%, and 50% yield respectively. We also tested the influence of electron-withdrawing substituents on the reaction outcome. A para-nitro substituent was well tolerated and the corresponding product **4m** was obtained in 59% yield. Both acyl- and ester substituents in meta- or para-position were tolerated and the desired products **4n–q** were obtained in 61%–81% yield. Finally, in order to probe whether the aryl iodide scope observed with propionic acid (**1b**) would be transferable to the other acids presented in the acid scope, a selection of representative aryl iodides was also tested with 2-methylvaleric acid (**1a**) as substrate (Scheme 3b). The corresponding products **3b** (74%), **3f** (77%), **3g** (81%), and **3j** (62%) were all obtained in yields comparable to the analogous products derived of propionic acid (**4b**, **4f**, **4g**, and **4j**).

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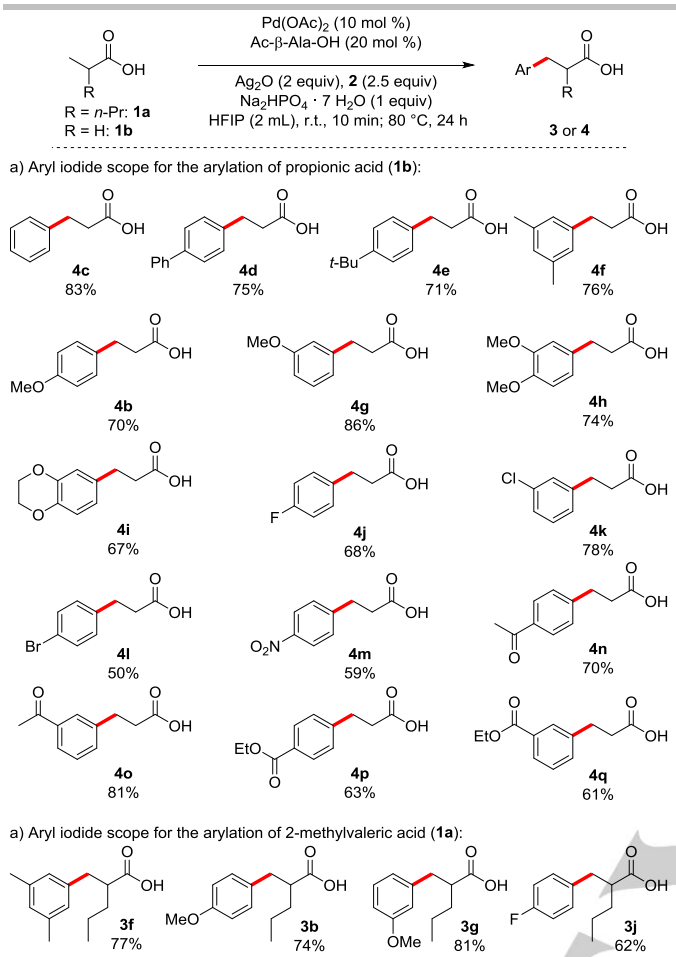
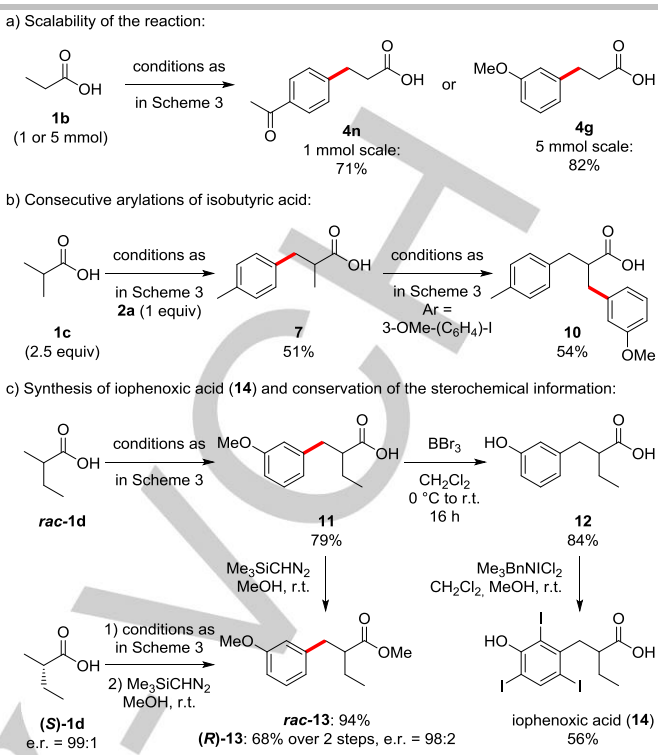


Scheme 3. Scope of the direct β-C(sp^3)–H arylation with respect to the aryl iodide using propionic acid (**1b**) and 2-methylvaleric acid (**1a**) as reaction partners. Unless noted otherwise the reactions were conducted on a 0.2 mmol scale.

In order to further probe the synthetic utility of our protocol, we began by testing the scalability of the process. Two representative products, **4n** (71% on a 1 mmol scale vs. 70% on a 0.2 mmol scale) and **4g** (82% on a 5 mmol scale vs. 86% on a 0.2 mmol scale), could be obtained with equal efficiency on an increased scale (Scheme 4a). We furthermore realized that our reaction conditions might serve as a general entry into non-symmetrical α-benzylhydrocinnamic acid derivatives from isobutyric acid (**1c**). In order to showcase this synthetic potential, the compound **7** was prepared by mono-arylation of isobutyric acid (**1c**) and then further transformed to the target compound **10** (Scheme 4b). The arylation of 2-methylbutanoic acid **1d** with 3-methoxyiodobenzene delivered acid **11** in 79% yield, which could be converted to the analogous methyl ester **13** by treatment with trimethylsilyldiazomethane (Scheme 4c). In order to probe the conservation of stereochemical information in our arylation process, we analogously synthesized the enantioenriched ester ***(R)*-13** with an enantiomeric ratio of 98:2 from commercially available ***(S)*-1d** (e.r. = 99:1). Acid **11** was easily de-methylated by treatment with boron tribromide, giving the phenol-derived acid **12** in 84% yield.



Scheme 4. Synthetic utility of the direct β-C(sp^3)–H arylation of aliphatic carboxylic acids.

Triple iodination of acid **12** using $Me_3BnNICl_2$ as a reagent allowed us to obtain iophenoxic acid (**14**), a compound employed in bait acceptance studies for wildlife research and formerly marketed under the name Teridax® as a cholecystographic agent.[13]

In summary, we have developed a generally applicable method for the β-C(sp^3)–H arylation of simple aliphatic acids. The method enables the arylation not only of α-branched and α-quaternary acids, but also of the particularly challenging propionic acid. The method was shown to display a broad scope with respect to the aryl iodide reagent and its applicability in a synthetic context was highlighted. Due to the ubiquity of aliphatic carboxylic acids in natural and synthetic compounds, we expect that this catalytic system will prove to be a valuable addition to the methods currently available to the synthetic community.

Furthermore, we foresee that this demonstration of a generally applicable β-C(sp^3)–H functionalization of aliphatic carboxylic acids, without the need for installing any more strongly coordinating directing group, will pave the way for the development of further analogous transformations employing other electrophilic coupling partners.

Experimental Section

General experimental procedure for the β-C(sp^3)–H arylation of aliphatic carboxylic acids: An oven dried 10 mL Schlenk tube was charged with the acid substrate **1** (0.2 mmol), aryl iodide **2** (0.5 mmol, 2.5 equiv), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol %), *N*-acetyl-β-alanine (5.2 mg, 0.040 mmol 20 mol %), Ag_2O (92.7 mg, 0.400 mmol, 2 equiv), $Na_2HPO_4{\cdot}7H_2O$ (53.3 mg, 0.199 mmol, 1 equiv), and HFIP (2 mL). The reaction vessel was tightly sealed and placed into an aluminum block with a tightly fitting recess on a

magnetic stirrer. The reaction mixture was stirred vigorously at room temperature for 10 minutes. The aluminum block was heated to 80 °C and stirring was continued at this temperature for 24 h. The reaction mixture was allowed to cool to room temperature and AcOH (0.1 mL) was added. The resulting mixture was filtered through Celite® using dichloromethane to complete the elution. The reaction mixture was concentrated under reduced pressure and the product was purified by silica gel column chromatography.

Acknowledgements

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Keywords: Arylation • Carboxylic Acids • C–H Activation • Palladium • Propionic Acid

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[11] The importance of *N*-acetyl-β-alanine as ligand becomes even more pronounced for propionic acid (**1b**) as substrate. A control experiment with *N*-acetyl glycine under otherwise optimized conditions resulted in an NMR-yield of 45%.

[12] Ortho-substituted aryl iodides were found to result in low yields of the desired products. For example a reaction between 2-methylvaleric acid (**1a**) and 2-methoxyiodobenzene resulted in an isolated yield of 40%.

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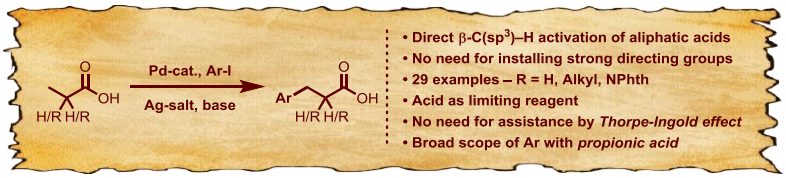

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Pd-Catalyzed β-C(sp³)–H Arylation of Propionic Acid and Related Aliphatic Acids

No Thorpe-Ingold effect required: A generally applicable Pd-catalyzed protocol for the β-C(sp³)–H arylation of propionic acid and its α-substituted derivatives was developed. The use of *N*-acetyl-β-alanine as ligand enabled a broad scope and synthetically useful yields with unsubstituted propionic acid as substrate for the first time.