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Quaternary Centers via Ni-Catalyzed Cross-Coupling of Tertiary Carboxylic Acids and Aryl Zinc Reagents

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Abstract

This work bridges a gap in the cross-coupling of aliphatic redox-active esters with aryl zinc reagents. Previously limited to primary, secondary and specialized tertiary centers, a new protocol has been devised to enable the coupling of general tertiary systems using Ni-catalysis. The scope of this operationally simple method is broad and can be used to simplify the synthesis of medicinally relevant motifs bearing quaternary centers.

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Graphical Abstract

Quaternary Center exchange. Fully substituted carbon centers bearing a carboxylate moiety can engage in decarboxylative cross coupling with aryl zinc reagents under Ni catalysis, leaving in their wake an arene group.

Keywords

quaternary centers; decarboxylative radical coupling; redox-active esters; practical protocols; tertiary acids

Recent interest in expanding rapid access to unique chemical space through the enablement of new cross-coupling methods has been enormous.¹ This, in part, is due to the retrosynthetic logic employed widely in discovery sciences towards medicines, agrochemicals, and materials, placing emphasis on convergent, modular disconnections.² Such pathways have been further stimulated by the myriad of vendors selling specialized building blocks rendering an almost limitless variety of subunits available to industrial chemists.³ Within this context, we were specifically drawn to the problem of constructing quaternary carbons, specifically those connected to an arene. Such motifs are found throughout the patent literature and are usually accessed through multi-step sequences (Figure 1A).⁴ Over the past decade, an explosion of interesting new techniques have emerged for achieving direct cross-couplings using alkyl halides,⁵ boronic acid derivatives,⁶ Grignard reagents,⁷ and most recently, olefins.⁸ While certainly useful, the substituents on such precursors (R¹, R², R³) are not easily programmable in addition to the fact that tertiary halides, borates, and Grignard reagents can be difficult to access. In contrast, a carboxylate coupling partner, of which thousands are available, are inherently diversifiable as R² and/or R³ substituents can be installed via sequential alkylation chemistry. Here, building on recent findings on the use of redox-active ester (RAE) derivatives for programmed radical cross-coupling,⁹⁻¹¹ we present a Ni-catalyzed protocol for the union of tertiary alkyl carboxylic acids with aryl zinc reagents.

Previous experience in Negishi-couplings of RAEs using bidentate amine ligands under Ni-catalysis showed that only primary and secondary systems were viable. Switching to an Fe-catalyzed system enabled the generation of quaternary centers but only in the context of bridged systems such as cubane, adamantane, and [2.2.2]-bicycles. Unstrained cyclic and acyclic tertiary RAEs remained a glaring limitation of both the Fe- and Ni-systems. Path-pointing studies by Gong⁵ and Molander^{6c} in their related cross-couplings aided initial feasibility screens suggesting the use of dicarbonyl-based ligands for Ni and Lewis acid as

additives. The optimum conditions, shown in Figure 1B for the conversion of tertiary RAE **1** to **3** (entry 1), emerged after extensive investigations that are fully summarized in the Supporting Information. The reaction was amenable to a one-pot procedure involving *in situ* activation (entry 2). Although the reaction required a TCNHPI- rather than the NHPI-based RAE (entry 3), the aryl zinc species could be either a diaryl or arylzinc halide, requiring 1.5 or 3.0 equiv., respectively (entry 4). Consistent with Molander's observations, the addition of ZnBr₂ had a slight but meaningful effect (*ca.* 10%) on the yield (entries 5 and 6) whereas a lower yield was observed in the presence of Mg-based analogs (entries 7 and 8). A solvent screen identified the DMI/THF mixture as superior to THF alone or DMF in place of DMI (entry 9). Lowering the catalyst loading to 10% decreased the reaction yield to 65% (entry 10). Finally, a screen of metal catalysts and ligands demonstrated that Fe- and Co-catalysts were not interchangeable (entry 11); while Ni(dpm)₂•xH₂O was optimum (entries 1, 12-17).

The conditions developed above proved to be general across a range of substrates as shown in Table 1 (>40 examples). The scope with regards to the aryl donor was first evaluated (Scheme 1A) to furnish adducts **3-23**. Notable amongst these examples is the functional group tolerance of the reaction with ethers (**4**, **15**, **17**), halides (**10**, **11**, **21**), benzofurans (**19**), and pyridines (**20**, **21**). Heterocycles and ortho-substituted arenes (**17**) diminished the yield somewhat but still provided serviceable quantities of product. Most notably, both electron rich and electron poor substituted arenes are viable coupling partners.

The vast scope of employable tertiary acids is described in Scheme 1B and features acyclic, cyclic, and those originating from natural products and medicines. High chemoselectivity is observed as a multitude of functional groups are compatible such as esters (**26**, **47**), carbamates (**27**), ethers (**28**, **30-33**, **39**), imides (**29**), sulfonamides (**38**, **42-44**), sulfones (**36**), enones (**46**), and even free alcohols (**46**). Simple acyclic acids as well as 3-, 4-, 5-, 6-, and 7-membered rings can also be enlisted. Of note here are the oxetane-derived products **30-33** that were prepared before in 2-4 steps¹² that can now be easily accessed in a single step from the commercial acid. The utility of the transformation was also demonstrated by the synthesis of product **28** derived from *Gemfibrozil*. Late-stage arylation of the triterpene 18-β-glycyrrhetic acid furnished product **46** without protection of the A-ring alcohol. The bridged system **47** can be viewed as a saturated mimic of a *para*-substituted benzene, useful for a variety of medicinal chemistry projects.¹³ The structure of products **8**, **23** and **41** were confirmed by X-Ray crystallographic analysis.

The retrosynthetic simplification enabled by this crosscoupling is further demonstrated with application to two reported medicinally promising scaffolds (Scheme 2). Thus, construction of the CCR5 ligand **51** (Scheme 2A) previously commenced with commercial piperidine **48** and proceeded through a five-step sequence to deliver **50**. Of those steps, only one productively made a C—C bond with the remainder dedicated to protecting group chemistry and redox-fluctuations. From a diversity standpoint, the chemists were necessarily wedded to a phenyl group as it originated from the commercial starting material. In contrast, inexpensive isonipecotic acid ester (**49**) could be processed through 3 simple steps, two of which generate key C—C bonds to deliver key intermediate **50**.^{4a,4b} Although the overall yield is not as high as the prior approach, diversity installation is completely modular and could, in principle, permit access to a whole range of substituents at the quaternary carbon

by simply changing alkylation and cross-coupling partners. In a similar vein, the anti-microbial compound **54** has previously been accessed using 2-electron retrosynthetic logic commencing from oxetane **52**.^{4c} Access to the quaternary center was enabled through a conjugate addition of an aryl boronic acid onto an α,β -unsaturated sulfone (**52'**). Subsequent deprotection/ S_N2 /desulfonylation delivered **54**. Alternatively, radical retrosynthesis¹¹ led to precursor **53** that could be subjected to decarboxylative cross-coupling followed by S_N2 to furnish the same product (**54**) in only two steps with an order of magnitude higher overall yield.

The coupling was also amenable to gram-scale as shown in Scheme 3. Without any modification of the standard conditions, piperidine **4** could be produced in similar yield (53%) to that run on 0.1 mmol scale (65% yield). Despite the advantages outlined herein, the reaction is not without limitations. For example, α -fluorinated and α -trifluoromethylated aliphatic acids were unreactive (only recovery of the starting acid was observed). Tertiary amino acids generally provided low yields (with the exception of **29**) and small strained bicyclic systems ([2.1.1] both fully carbon and heteroatom substituted) did not function well. This chemistry is also currently limited to aryl zinc reagents as alkyl variants gave low yield.

As one of the most ubiquitous functional groups known, carboxylic acids are an ideal starting point for cross-coupling chemistry. When coupled to alkylation or other α -functionalization methods, tertiary acids that are not already commercial are easily prepared in a modular fashion. The simple protocol delineated herein permits simple thermal, scalable access to convert such building blocks to diverse arene-flanked quaternary centers with demonstrable value to society.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A. Tertiary Alkyl Electrophiles: Precursors for Quaternary Centers

B. Optimization of Ni-catalyzed Arylation with Tertiary RAEs^a **Figure 1.**

(A) Access to quaternary centers via cross coupling: Prior art. (B) Optimization on Ni-catalyzed cross coupling of tertiary RAEs with arylzinc reagents. ^a0.1 mmol. ^bYield determined by ¹H NMR with CH₂Br₂ as an internal standard. ^cIsolated yield. See Supporting Information for details. DMI = 1,3-dimethyl-2-imidazolidinone, ND = not detected. dpm = 2,2,6,6-tetramethylheptane-3,5-dione, acac = acetylacetone, dibm = *i*-PrCOCH₂CO*i*-Pr, hfac = hexafluoroacetylacetone, fdh = 1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedione, btfa = 3-benzoyl-1,1,1-trifluoroacetone, dbm = dibenzoylmethane Ts = tosyl, TCNHPI = *N*-hydroxytetrachlorophthalimide, NHPI = *N*-hydroxyphthalimide.

Scheme 1.

Scope of the Ni-catalyzed arylation of tertiary RAEs. Reaction conditions: Redox-active ester (1 equiv), Ni(dpm)₂·xH₂O (20 mol%), Ar₂Zn (1.5 equiv), ZnBr₂ (1 equiv) in THF/DMI (4:3) at rt for 12 h. [Isolated] refers to yields from the isolated redox-active ester, and [in situ] refers to yields from the carboxylic acid. *a* With Ni(dpm)₂·xH₂O (40 mol%) and Ar₂Zn (2.5 equiv). *b* With Ni(dpm)₂·xH₂O (40 mol%) and Ar₂Zn (2.5 equiv) at 60 °C. *c* With Ni(dpm)₂·xH₂O (40 mol%) and Ar₂Zn (2.5 equiv) in THF/DMF at 60 °C. *d* With Ni(dpm)₂·xH₂O (20 mol%) and Ar₂Zn (2.5 equiv). *e* In situ from carboxylic acid (1.0 equiv.), TCNHPI (1.1 equiv.), DIC (1.1 equiv.) and DMAP (0.1 equiv.). Ts: tosyl; TBS: *tert*-

butyldimethylsilyl; Boc: *tert*-butyloxycarbonyl; Phth: phthalimido; DIC: *N,N*-diisopropylcarbodiimide.

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A Modular, Efficient Synthesis of CCR5 Ligand (**51**) **B** Convergent Synthesis of Antimicrobial (**54**) **Scheme 2.**

Radical retrosynthesis simplifies the synthesis of bioactive compounds from the patent literature.