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Efficient and scalable arylation of bicyclic lactones to form quaternary centers using conventional and microwave radiation

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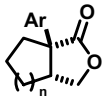
Abstract—Easily accessible bicyclic lactones were efficiently arylated under modified Hartwig and Buchwald conditions to form quaternary aryl centers with complete *cis* selectivity. This series is notable in that unreactive substrates, including sterically-demanding *ortho*-substituted aromatic compounds, enjoyed significant rate acceleration under microwave radiation. Additionally, it was noted that the reactions could be accomplished under standard anaerobic conditions and on multi-gram scale.

Assembling quaternary centers substituted with an aryl group usually entail starting with an aryl-substituted synthon and adding the other alkyl elements. For any series of analogs, this requires that the aryl group be fixed early in the synthesis. However, during the course of our medicinal chemistry efforts it became desirable to build bicyclic lactone systems quickly that were differentially arylated at the alpha position.



n = 1, 2

Given the recent advances in ester arylation, we speculated that direct arylation of the precursor lactone should be possible by the methods of either Buchwald[1] or Hartwig.[2] Indeed, the lactones were arylated efficiently using either condition. Further, under our improved conditions, the reactions were scalable to several grams and required no special conditions other than standard anaerobic laboratory techniques. Ultimately, it was found that microwave radiation could increase the reaction yields significantly for unreactive substrates, including sterically-demanding *ortho*-substituted aromatic compounds.

The palladium-catalyzed addition of aryl halides and sulfonates to carbon enolates is now well precedented and employed. This reaction has been applied to ketones, esters, amides, and monocyclic lactones. Thus far, however, no examples of bicyclic lactones have been reported.

The starting lactones were easily accessed via the commercially-available diacid anhydrides by sodium borohydride[3] or LAH[4] reduction. Alternatively, enantiomerically-enriched lactones could be obtained via the Cinchona alkaloid-mediated selective anhydride opening procedures of Deng and Chen[5] and Bolm et al.,[6] esterase catalyzed differentiation,[7] or the HLADH-catalyzed oxidation of the diol.[8]

Happily, the reaction of these lactones proceeded well using only slight variations of the reported conditions.[2a] During the course of our optimizations, we made several observations relating to the requirements of the reaction. All of the HMDS bases were surveyed with little notable difference, but LiHMDS was selected as a suitable replacement for the more bulky dicyclohexylamine. The availability and ease of use of the commercial solution was found preferable, despite the observation that some of the aryl bromide was consumed in a reaction with the HMDS.[9] However, it was not determined whether this occurred prior or subsequent to the end of the carbon arylation.

Keywords: Arylation; Palladium; Microwave; Quaternary center.
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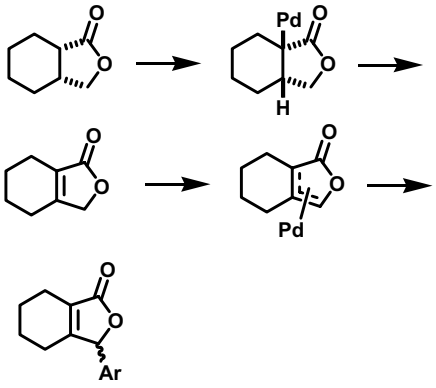
The reaction could be conveniently run at room temperature, but we found it useful to heat some of the mixtures (50 °C) to ensure full conversion at desirable reaction rates. Dry-box manipulations and Schlenk-apparatus were unnecessary as oven-dried glassware and syringes were adequate for good yields. The reactions could be run under nitrogen pressure or in sealed vessels.

Also noted during our studies was the relatively low dependence of the yield on changing the order of addition or small variances in the reagent ratios. Thus, the ratio of substrate to bromide could be varied based on other considerations such as cost, availability, and ease of removal. The reaction could also be run in the absence of additional solvent. However, no advantage was noted in ease of workup or yield.

The optimized reaction[10] was tested on a five- and six-membered bicyclic γ-lactone with aromatic groups of varying electronic nature (Table 1). As expected, due to the rigidity of the system, only the *cis* product was observed. In most cases, condensation of these lactones with aryl bromides proceeded to give the arylated lactones in good yield. Electron-donating and -withdrawing aromatics, and heteroaromatics were tolerated. However, *ortho*-substituted aromatics were not coupled under these standard conditions. Fortunately, the reaction was amenable to scale as exemplified by entries 2, 5, and 11, denoting multi-gram quantities of starting lactone.[11]

Some side-products were observed by GC–MS (e.g., biaryls and anilines) but were efficiently removed via aqueous workup and column chromatography. In one case, a small amount of side-product was isolated that had a mass of 2 AMU less than expected. It was determined by NMR[12] that this product was likely the unsaturated analog of the expected product arylated at the gamma position. We envision that this product could arise from a competing reaction pathway, wherein the palladium enolate undergoes a β-hydride elimination to give an enone. This enone, could then be deprotonated and arylated.

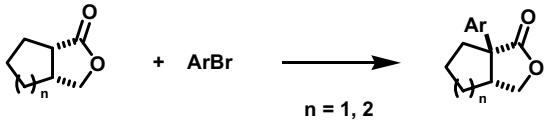


Arylation of the five-membered ring lactone (Table 1, entry 12) was too slow for a reasonable comparison at room temperature. Under heating conditions (80 °C overnight), the starting lactone was consumed, but the product mixture was plagued by the appearance of inseparable side-products. While optimization of the original conditions was a possibility, we chose to explore microwave irradiation as an alternative energy source.[13] Fortunately, this reaction is amenable to microwave assistance, which enabled much shorter reaction times (10 min).

As can be seen in Table 2, the five-membered ring systems enjoyed an increase in yield using microwave irradiation. Most satisfying was the formation of *ortho*-substituted aromatic compounds, albeit in modest yield. The six-membered ring systems gave varied results under these conditions. The underlying cause was not clear from these studies, but it may be that the reaction conditions employed were too harsh for this system.

In conclusion, we have developed methods for arylating a six-membered bicyclic γ-lactone under standard

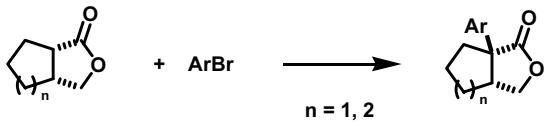
Table 1. Conventional lactone arylation results



Entry	*n* =	ArBr	Scale (mmol)	Yield (%)
1	2	PhBr	1	88
2	2	PhBr	50	67
3	2	4-MeOPhBr	1	36
4	2	3-MeOPhBr	1	60
5	2	3-MeOPhBr	71	60[a]
6	2	2-MeOPhBr	1	[b]
7	2	3-FPh	1	65
8	2	2-Br pyridine	1	71
9	2	3-Br pyridine	1	35[c]
10	2	3,4-DiClPhBr	1	30
11	2	3,4-DiClPhBr	30	48
12	1	PhBr	1	[d]

[a] Side-product isolated in 7% yield.
[b] No product, but multiple side-products observed.
[c] Yield reduced by multiple purifications.
[d] Product not isolable, low conversion.

Table 2. Microwave arylation results



Entry	*n* =	ArBr	Scale (mmol)	Yield (%)
1	1	PhBr	1	49
2	1	4-MeOPhBr	1	62
3	1	3-MeOPhBr	1	59
4	1	2-MeOPhBr	1	25
5	2	PhBr	1	51
6	2	4-MeOPhBr	1	41
7	2	3-MeOPhBr	1	15
8	2	2-MeOPhBr	1	8[a]

[a] M-2 side-product is major.

laboratory conditions that are amenable to 1–70 mmol scale. Further, we have demonstrated that microwave irradiation expands the scope of this reaction to include a five-membered bicyclic lactone and *ortho*-substituted aromatics. Finally, this class of compounds has already proven useful in our medicinal chemistry efforts, which will be reported in a separate publication.

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10. *1 mmol scale.* The lactone was weighed out into a flame-dried vial. The catalyst was added and covered in anhydrous toluene before the flask was purged with nitrogen and sealed. The phosphine was then added as a solution in toluene and stirred for 2 min. To this was added LiHMDS and, finally, the aromatic bromide, leading to a slight exotherm and precipitation of the salt. After 16 h at 50 °C, the solution was diluted with hexanes and 10% aqueous HCl and stirred for 10 min. The organic layer was separated, dried, and evaporated. The residue was separated by silica gel chromatography to yield the aromatic lactone.
11. *Multi-gram scale procedure. 7a-Phenyl-hexahydro-isobenzofuran-1-one.* To a flame-dried 250 mL round bottom flask were added $Pd(dba)_2$ (368 mg, 1 mol %) and toluene. The vessel was purged with nitrogen and sealed before tri-*t*-butylphosphine (704 μL, 1 M in toluene, 1.1 mol %) was added via syringe, followed by phenyl bromide (5.4 mL, 51.27 mmol) as a solution in toluene (15 mL). LiHMDS (64 mL, 1.3 equiv) was added and the light brown solution was stirred at ambient temperature for 15 min. Hexahydro-isobenzofuran-1-one (10 g, 1.3 eq) was added dropwise as a solution in toluene (20 mL). At this point, an exotherm was noted followed by the formation of a light colored precipitate. The mixture was allowed to stir at ambient temperature overnight (16 h) and then partitioned between hexane and, in succession, 10% aqueous HCl, 10% aqueous K_2CO_3, and brine. The volatile components were removed in vacuo to give the crude arylated lactone as a brown-green oil (12.6 g). The separation of the unreacted lactone using a 120 g Redisep cartridge gave the title compound as a yellow oil (7.40 g, 67%).
^{1}H NMR ($CDCl_3$, δ): 7.4–7.2 (m, 5H), 4.05 (dd, 1H), 3.90 (dd, 1H), 2.8 (m, 1H), 2.3 (m, 1H), 2.0 (m, 1H), 1.8–1.3 (m, 6H). ^{13}C NMR ($CDCl_3$, δ, mult): 178.6 (0), 140.5 (0), 128.8 (1), 127.3 (1), 126.3 (1), 70.3 (2), 52.5 (0), 41.0 (1), 34.2 (2), 27.5 (2), 23.4 (2), 23.2 (2).
12. *o-Methoxy side-product: 4,5,6,7-tetrahydro-3-(2-methoxyphenyl)isobenzofuran-1(3H)-one.* GC–MS $m/z = 244$. ^{1}H NMR ($CDCl_3$, δ): 7.4–6.9 (m, 5H), 6.2 (s, 1H), 3.95 (s, 3H), 2.3 (m, 3H), 2.0 (m, 1H), 1.7 (m, 4H). ^{13}C NMR ($CDCl_3$, δ, mult): 174.4 (0), 164.9 (0), 157.1 (0), 130.0 (1), 126.6 (1), 125.7 (0), 123.7 (0), 121.1 (1), 110.9 (1), 79.3 (1), 55.7 (3), 23.4 (2), 21.8 (2), 21.7 (2), 20.2 (2).
13. *Microwave reaction.* The lactone was weighed out onto a vial along with the palladium catalyst and covered with toluene. At this point, the vessel was purged with nitrogen and sealed. The phosphine solution was added by syringe and stirred for 2 min, followed by LiHMDS and the aromatic bromide. The reactions were carried out using the Emrys Optimizer microwave instrument from Biotage. The temperature was set to 140 °C for 600 s, with no fixed hold time, and the sample absorption was set to normal. The mixture was stirred during the course of the reaction, but there was no pre-stirring interval set. After cooling, the reaction was quenched with 2 mL of 3 M aqueous HCl and stirred for 10 min. After removal of the aqueous layer, the organic layer was diluted with hexanes and washed with HCl. The organic layer was then dried over Na_2SO_4 and filtered. Finally, the solvent was removed in vacuo and the residual oil was separated on silica gel.