

Communication

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Palladium-Catalyzed Carbonylative Couplings of Vinylogous Enolates: Application to Statin Structures

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Supporting Information Placeholder

ABSTRACT: The first Pd-catalyzed carbonylative couplings of aryl and vinyl halides with vinylogous enolates is reported generating products derived from C–C bond formation exclusively at the γ -position. Good results were obtained with a dienolate derivative of acetoacetate (1,3-dioxin-4-one). These transformations occurred at room temperature and importantly with only stoichiometric carbon monoxide in a two-chamber reactor. The methodology was applied to the synthesis of two members of the statin family generating the *cis*-3,5-diol acid motive by a γ -selective carbonylation followed by a *cis*-stereoselective reduction of the 3,5-dicarbonyl acid intermediates.

The palladium-catalyzed arylation or vinylation of enolizable carbonyl and related compounds represents a viable and useful C–C bond forming reaction widely applied in synthetic organic chemistry.¹ Notably, the groups of Buchwald² and Hartwig,³ among others,⁴ have identified useful catalytic conditions for this synthetic transformation involving enolate or enolate-type intermediates. The majority of this work has been focused on the installment of an aryl or vinyl substituent in the α -position, but few reports have been made extending the methodology to the γ -position of α , β -unsaturated ketones⁵ and esters,⁶ thereby including vinylogous enolates in the repertoire of reactive intermediates.

Recently, we reported a useful carbonylative version of the α arylation allowing access to 1,3-diketones,⁷ β -ketoesters⁸ and amides,⁹ as well as α -nitroketones,¹⁰ 3-acyl-2-oxindoles,¹¹ and others.^{12,13} An intriguing question therefore arose as to whether vinylogous enolates also could become useful substrates in this carbonylative arylation or vinylation, and if so, would carbonylation likewise be directed to the γ -position? Furthermore, if such a transformation could be adapted to the use of acetoacetate dienolates or dienol silyl ethers, this methodology could provide a carbonylative version towards the common *cis*-3,5-diol acid pharmacophore of a range of HMG-CoA reductase inhibitor drugs, better known as the family of statins (Scheme 1).¹⁴

In this communication, we report on the development of such a Pd-catalyzed carbonylative protocol, which provides a direct entry to 3,5-dicarbonyl acids from the coupling of a dienolate equivalent of acetoacetate to a variety of functionalized aryl or vinyl iodides. The reactions occur in good yields and with complete γ -selectivity and can be performed using only stoichiometric amounts of carbon monoxide (CO). Moreover, this methodology allows access to an alternative carbon isotope labeling strategy of the statin family.

Scheme 1. Strategy for Carbonylative Coupling of Vinylogous Enolates



In initial studies, efforts were directed to identifying suitable reaction conditions for the carbonylative coupling of the dianion of ethyl acetoacetate with 4-iodoanisole. A two-chamber reactor system was employed with SilaCOgen as the carbon monoxide source.¹⁵ After extensive screening, the desired diketoester **1** could be generated (Scheme 2), but at best as a 1:7 mixture with the side-product originating from the direct coupling without CO incorporation. Alternatively, the silyl enol derivative **2** proved more promising and with better selectivity. Treatment of **2** with NaHMDS (2 equiv) and then injection into a two-chamber system containing Pd(dba)₂, Xantphos and 4-iodoanisole provided, according to ¹H-NMR analysis, the desired tricarbonyl derivative, though as a mono-enol tautomer. Although this compound proved difficult to isolate, its treatment with hydrazine led to the more manageable pyrazole **3**. Nevertheless, efforts to improve this



two-step yield to over 50% proved unrewarding.¹⁶

We suspected that the high basicity and hence instability of the carbon nucleophile could be the cause of the low carbonylative coupling efficiency. Subsequently, efforts were turned to 2,2,6-trimethyl-4H-1,3-dioxin-4-one (4), which immediately under the screening process proved to be superior to 2^{17} As can be seen from Table 1, entry 1, NaHMDS could be replaced with LiHMDS,¹⁸ and only a slight excess of the dioxin-4-one compared to 4-iodoanisole was required this time. With Xantphos as the ligand, an excellent conversion and the isolation of 71% of ketone 5 was obtained. Importantly, no products from the direct α arylation were detected. Use of other bases provided inferior results (entries 2-5). Testing of other bidentate ligands was also less rewarding (entries 6-8), although application of DiPrPF provided a satisfactory NMR yield of 5 (entry 8). Other solvents such as dioxane, toluene or acetonitrile led to inferior conversion rates (results not shown). Finally, reduction of the catalyst loading to 3 mol% did not effect the yield (entry 9) and by decreasing the reaction time to 6 h, a satisfactory 82% isolated yield of 5 could be secured (entry 11).

 Table 1. Screening of Conditions for the Carbonylative

 Coupling of 4 with 4-Iodoanisole

Chamber A (COware) Pd(dba)₂ (5 mol%), Ligand (5 mol%) Base (2.2 equiv) THF, rt, 18 h Chamber B (SilaCOgen) Ph2MeSiCO2H (1.3 equiv) MeO °0 4 (1.1 equiv) CsF (10 mol%) THF, rt, 18 h Yield Conv. Entry Ligand Base [%]^{*c*} [%]" 95 (71)^b 1 Xantphos LiHMDS 100 2 Xantphos LiOtBu 86 58 3 NaOtBu 100 0 Xantphos 4 Xantphos Cs₂CO₃ n.d.' 0 5 Xantphos K₂CO₃ 0 0 6 DPPP LiHMDS 0 0 DPPF 7 LiHMDS n.d. 52 8 96 DiPrPF LiHMDS n.d. 9^d Xantphos LiHMDS 100 $99(71)^{b}$ 10^{*d*,*e*} 100 >95 Xantphos LiHMDS 11^{*d,e,f*} Xantphos LiHMDS 100 99 (82)^b

^{*a*} Determined by ¹H NMR using MeNO₂ as an internal standard. ^{*b*} Isolated yield. ^{*c*} Not determined. ^{*d*} 3 mol% of Pd(dba)₂ and ligand. ^{*e*} Reaction time of 6 h. ^{*f*} CsF (1.3 equiv).

Scheme 3. Carbonylative Vinylogous Couplings of 4 with Aryl and Vinyl Iodides^a



^{*a*} All reactions were run in a two-chamber system on a 0.5 mmol scale (c = 0.167 M). ^{*b*} Reaction time of 18 h. ^{*c*} Triphenylphosphine (6 mol%) was used and LiHMDS (1.0 M in hexane) was added at 0 °C.

With good carbonylative and y-selective coupling conditions identified, we next scoped out the reaction with a number of substituted arvl or vinvl iodides, the results of which are depicted in Scheme 3. The developed conditions proved equally effective for substrates bearing either electron donating or electron withdrawing substituents with yields ranging between 61-84%. Satisfyingly, ortho-substituents on the aryl ring, including fluoride, bromide and a methoxy group were also well tolerated (compounds 20, 21, and 22), although prolonged reaction times (18 h) were required for efficient conversion. For similar couplings to vinyl iodides, direct coupling of 4 to the activated alkene proved to be a serious side product. Subsequently, a ligand screening was undertaken, revealing PPh3 to be an appropriate ligand in couplings to vinyl iodides as well as suppressing the direct coupling (see Supporting Information). In this way, compounds 23 and 24 could be furnished in isolated yields of 89% and 84%, respectivelv.

Additionally, we applied this methodology on a range of substituted dioxinones as depicted in Scheme 4. When a substitu-

ent is placed on the γ -position of the dioxinone, the reactivity of the entering nucleophile decreases, since the yields drop significantly for both aryl iodides and vinyl iodides (compounds **25**, **27** and **29**). However, when the substituent was placed on the α position of the dioxinone, an excellent yield of 93% was obtained with iodoanisole and a good yield of 59% was obtained for the (*E*)-1-(2-iodovinyl)-4-methoxybenzene, although with the necessity of adding the base at 0°C for the latter (compounds **26** and **28**, respectively).

Scheme 4. Carbonylative Coupling with Substituted Dioxinones



^{*a*} 3.0 mol% of Xanthphos was used for aryl iodides and 6.0 mol% of PPh₃ was used for vinyl iodides. ^{*b*} LiHMDS (1.0 M in hexane) was added at 0 °C.

In light of the suitability of vinyl iodides as the electrophilic partner for the Pd-catalyzed carbonylative coupling with 2,2,6trimethyl-4H-1,3-dioxin-4-one (4), we next turned to apply this strategy for the synthesis of HMG-CoA reductase inhibitors. Initial efforts were directed to the drug candidate developed by Merck in the early 90's for the treatment of hypercholesterolaemia (Scheme 5). (E)-4'-Fluoro-2-(2-iodovinyl)-3,3',5-trimethyl-1,1'biphenyl (31) was readily accessible from commercially available 2-bromo-4,6-dimethylaniline (30) in four steps.²⁰ The Pdcatalyzed carbonylative coupling was then conducted leading to the formation of the dioxinone 32 in a good isolated yield of 57%. From intermediate 32, a two-step procedure could be applied to achieve the tert-butyl ester 33 of the HMG-CoA reductase inhibitor as a racemic mixture. The dioxinone was opened by thermal decomposition and trapped with tert-butanol. Diastereoselective reduction using sodium borohydride combined with diethylmethoxyborane as the chelating agent afforded the syn-1.3-diol 33 with complete diastereoselectivity in an overall yield of 55% yield for two steps.21

With the successful obtainment of compound **33**, we then considered the possibility of exploiting the developed method towards the specific carbon isotope labeling of the statin family, and in particular the commercially available drug, Pitavastatin. As illustrated in Scheme 6, (E)-2-cyclopropyl-4-(4-fluorophenyl)-3-

(2-iodovinyl)quinoline (**35**) was readily prepared in 6 steps from 2-nitrobenzoic acid (**34**).²² Subsequently, its participation in the Pd-catalyzed carbonylative coupling using ¹³C-SilaCOgen produced the ¹³C-labeled dioxinone **36** in an excellent isolated yield of 85%.²³ Afterwards, dioxinone opening was accomplished using ethanol in toluene followed by the *syn*-diastereoselective reduction of the two ketones, ultimately affording the ¹³C-labeled ethyl ester of (±)-Pitavastatin **37** in a 31% isolated yield over two steps.²⁴

Scheme 5. Synthesis of the *t*Butyl Ester of the HMG-CoA Reductase Inhibitor 33.



Scheme 6. Synthesis of (±)-¹³C-Pitavastatin Ethyl Ester



In conclusion, we have for the first time expanded the usefulness of the Pd-catalyzed carbonylation couplings to a new class of nucleophiles, namely vinylogous enolates. In particular, the dienolate derivative of acetoacetate could be coupled to a range of aryl and vinyl iodides providing 3,5-dicarbonyl acids with complete γ -selectivity. Furthermore, the carbonylation reactions could be performed at room temperature and with stoichiometric carbon monoxide. Finally, we could adapt this methodology to the synthesis of statins including specific carbon isotope-labeling. Further work is now ongoing to examine other vinylogous enolates as substrates for this interesting three-component coupling reaction.

ASSOCIATED CONTENT

Supporting Information

Copies of ¹H NMR and ¹³C NMR spectra for all coupling products, as well as details on experimental procedures. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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Notes

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The authors declare the following competing financial interest(s): Anders T. Lindhardt and Troels Skrydstrup are co-owners of SyTracks a/s, which commercializes the two-chamber technology.

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(16) A reagent ratio of 4-iodoanisole:2:NaHMDS of 1:2:4 proved to be the best ratio for obtaining the reported yield of compound **3**.

(17) The γ -selective alkylation and chlorination of the dienolate of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one is known. For example see: (a) Smith III, A. B.; Scarborough Jr., R. M. *Tetrahedron Lett.* **1978**, *19*, 4193. (b) Boeckman Jr., R. K.; Perni, R. B.; Macdonald, J. E.; Thomas, A. J. Org. Synth. **1988**, *66*, 194.

(18) We have earlier shown that LiHMDS is not an effective base for the Pd-catalyzed carbonylative α -arylation of simple ketones, whereas NaHMDS is (see ref. 7 a). We are currently examining the role of the counterion in carbonylation reactions with other enolates in order to understand this effect.

(19) Despite extensive screening of palladium sources, ligands, solvents and bases, no conversion was observed for the corresponding aryl bromides. On the other hand, compound **24** could be obtained from the vinyl bromide equivalent, although at best with an NMR yield of approx. 50%.

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(23) The 2.2 equivalents of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and 2.2 equivalents of LiHMDS were pre-mixed at 0 °C prior to the addition to the reaction mixture. See Supporting Information for the detailed procedure. The addition of 2.2 equivalents of LiHMDS to the reaction mixture at room temperature did not afford dioxinone **35**, probably because of the acidity of the cyclopropylic proton at the 2-position of the quinoline.

(24) The low yield is explained by the competitive 1,6-addition of the hydride compare to the 1,4-addition during the reduction step, leading to a 2/1 mixture of alkene and alkane, which are difficult to separate.

