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Optimization of a Pd-catalyzed intramolecular α-arylation synthesis of tricyclo-[7.3.1.0^{2,7}]-trideca-2,4,6-trien-13-ones

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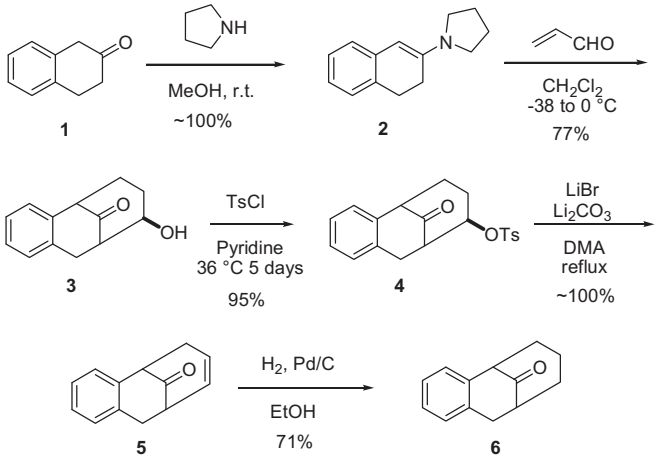
ABSTRACT

We have optimized the Pd-catalyzed intramolecular α-arylation of 2-(2-halo-benzyl)-cyclohexanones and found that the use of 2-(dicyclohexylphosphino)-2′,4′,6′-tri-*i*-propyl-1,1′-biphenyl (X-Phos) as an added ligand led to a reproducible, efficient, and scalable synthesis of tricycle-[7.3.1.0^{2,7}]-trideca-2,4,6-trien-13-ones.

Structurally complex polycyclic structures have long inspired synthetic chemists due to their presence in a wide variety of biologically active natural products. In the pharmaceutical industry, polycyclic structures are often targeted during the drug discovery process as a strategy to improve the potency and/or pharmacokinetic properties of a series of analogs through reduced conformational flexibility. We were interested in the tricyclo-[7.3.1.0^{2,7}]-trideca-2,4,6-trien-13-one **6** as a key intermediate for a medicinal chemistry program and required a concise synthetic route capable of producing multi-gram quantities for further elaboration. Our first-generation route (Scheme 1) involved a lengthy synthetic sequence starting with the β-tetralone **1**.[1] While >50 g of **6** could be prepared via this route, we recognized that this route was laborious, inefficient, and not readily amenable for the rapid investigation of the structure–activity relationships (SARs) around the tricyclic core ring structure. Consequently, we sought a route that would be shorter in length, more atom efficient, and readily amenable to SAR studies around the tricyclic core.

Muratake et al. have reported a concise synthesis of **6** through a Pd-catalyzed intramolecular ketone α-arylation of 2-(2-bromobenzyl)-cyclohexanone **7** (Fig. 1).[2] Since this route represented a substantial improvement over the original synthesis, we attempted to



Scheme 1. First generation synthesis of the tricycle-[7.3.1.0^{2,7}]-tridec-2,4,6-trien-13-one core.

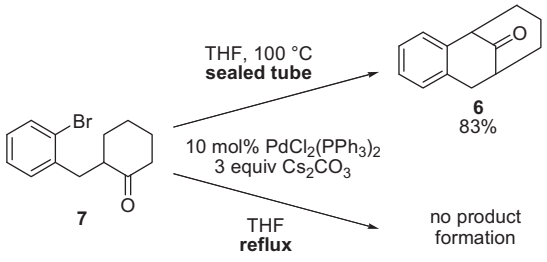


Figure 1. Initial attempts to realize intramolecular ketone α-arylation of 2-(2-bromobenzyl)-cyclohexanone **7**.

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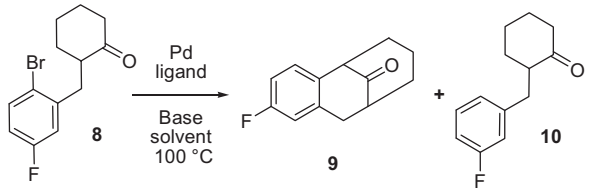
repeat their results. Accordingly, we were pleased to find that the treatment of **7** with 10 mol % $PdCl_2(PPh_3)_2$ and 3 equiv of Cs_2CO_3 in THF in a sealed tube at 100 °C afforded the desired tricyclic ketone **6** in 83% yield on a 50 mg scale. However, we were unsuccessful in reproducing these results at reflux under atmospheric pressure conditions. Since sealed tube conditions were unlikely to support the synthesis of the multi-gram quantities of ketone **6** that would be required to support our medicinal chemistry efforts, we embarked on an optimization of the Pd-catalyzed intramolecular ketone α-arylation of **7**. Iwama and Rawal have recently reported the successful Pd-catalyzed intramolecular α-arylation of trimethysilyl enol ether derivatives using a $Pd_2(dba)_3$/*t*-Bu_3P catalyst system.[3] While directly applicable to the synthesis of tricyclo-[7.3.1.$0^{2,7}$]-trideca-2,4,6-trien-13-ones, we sought to avoid the required formation of the trimethylsilyl enol ether and further investigated the cyclization of the parent ketone.[4,5] Recently, Khartulyari and Maier have reported success in the intramolecular α-arylation of ketones to prepare structurally similar benzomorphan derivatives in moderate yields using the $Pd(dba)_2$/*t*-Bu_3P catalyst system.[6] This report emerged after our studies were completed, but indicates that others have also succeeded in avoiding the preliminary formation of silyl enol ethers.

Initial reaction optimization studies were conducted with 2-(2-bromobenzyl)-cyclohexanone **7** (Table 1).[7] Interestingly, heating the reaction mixture in the non-polar solvent toluene at reflux gave no detectable product (entry a), which was at odds with the results reported by Muratake et al.[2] However, switching to a more polar solvent, such as DMF, did afford the desired product **6** in low yield when heated at 80 °C (entry b). Encouragingly, higher reaction temperatures led to a greatly improved 72% yield of **6** (entry c). Other polar solvents, such as 1,4-dioxane or DMA, were also successful in promoting the α-arylation reaction in moderate to good yields (48–72%, entries d and e). The use of DMF as a solvent proved to be scalable, as a 16 mmol scale reaction afforded **6** in 66% yield (entry f).

While acceptable yields of **6** under non-sealed tube conditions were obtained by simply using more polar solvents, such as DMF and DMA, we were concerned about the isolation of **6** from large quantities of DMF or DMA. Furthermore, the use of 3 equiv of Cs_2CO_3 on multi-gram scale could be problematic and expensive. Consequently, we further investigated the optimization of the reaction conditions with the goal of identifying reaction conditions utilizing a less expensive base and a more tractable solvent. Because the electron-rich phenyl ring present in **6** was viewed as a potential metabolic liability, we chose to install an electron-withdrawing fluorine substituent on the phenyl ring and utilize substrate **8** in our optimization experiments. All reactions were performed in a parallel fashion in a Radley reaction carousel (Table 2). While low yields of the desired cyclization product **9** were obtained in refluxing THF with Cs_2CO_3 as a base (entry a); Cs_2CO_3 in toluene resulted in no reaction (entry b). The use of more soluble inorganic bases in toluene afforded low yields of **9** (entries c and d), while amine bases completely inhibited the reaction (entry e). The des-bromo compound **10** was identified as the major by-product in these reactions, presumably as a result of competitive proteo-reductive elimination in the catalytic cycle. A solvent survey with K_3PO_4 as the base indicated more polar solvents, such as 1,4-dioxane, DME, and DMF, afforded higher yields of **9** (entries f–h). A catalyst survey determined that $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ gave equal yields of product, while $Pd(t\text{-}Bu_3P)_2$, $PdCl_2$(dppf), and the cationic POPd and $POPd_2$ catalysts[8] gave no reaction (entries i–m). The failure of $Pd(t\text{-}Bu_3P)_2$ to catalyze the reaction is significant, given the successful use of in situ-prepared $Pd(t\text{-}Bu_3P)_2$ by Iwama & Rawal and Khartulyari & Maier in similar reactions.[3,6]

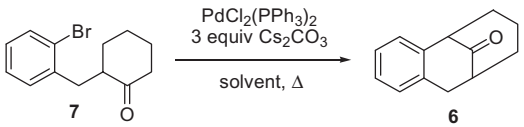
Table 2
Optimization of intramolecular α-arylation of ketone **3**



Entry	Pd catalyst[a]	Ligand[b]	Base[c]	Solvent	Yield (%)
a	$PdCl_2(PPh_3)_2$	—	Cs_2CO_3	THF	39 **9**
b	$PdCl_2(PPh_3)_2$	—	Cs_2CO_3	$PhCH_3$	NR
c	$PdCl_2(PPh_3)_2$	—	NaO*t*-Bu	$PhCH_3$	14 **9**, 13 **10**
d	$PdCl_2(PPh_3)_2$	—	K_3PO_4	$PhCH_3$	34 **9**, 21 **10**
e	$PdCl_2(PPh_3)_2$	—	Et_3N	$PhCH_3$	NR
f	$PdCl_2(PPh_3)_2$	—	K_3PO_4	1,4-Dioxane	53 **9**
g	$PdCl_2(PPh_3)_2$	—	K_3PO_4	DME	50 **9**
h	$PdCl_2(PPh_3)_2$	—	K_3PO_4	DMF	63 **9**
i	Pd $(PPh_3)_4$	—	K_3PO_4	$PhCH_3$	32 **9**
j	$Pd(Pt\text{-}Bu_3)_2$		K_3PO_4	$PhCH_3$	NR
k	$PdCl_2$·dppf	—	K_3PO_4	$PhCH_3$	NR
l	POPd	—	K_3PO_4	$PhCH_3$	NR
m	$POPd_2$	—	K_3PO_4	$PhCH_3$	NR
n	$Pd(OAc)_2$	11	K_3PO_4	$PhCH_3$	40 **9**
o	$Pd(OAc)_2$	12	K_3PO_4	$PhCH_3$	67 **9**
p	$Pd(OAc)_2$	13	K_3PO_4	$PhCH_3$	84 **9**
q	$Pd(OAc)_2$	14	K_3PO_4	$PhCH_3$	68 **9**
r	$Pd(OAc)_2$	15	K_3PO_4	$PhCH_3$	NR

[a] Pd catalyst loading of 10 mol %.
[b] Ligand loading of 20 mol %.
[c] 3 equiv of base.

Table 1
Solvent affects on the Pd-catalyzed intramolecular ketone α-arylation of substrate **7**



Entry	Scale (mmol)	Mol % Pd catalyst	Solvent	Temp (°C)	Yield (%)
a	10	20	Toluene	Reflux	NR[a]
b	19	8	DMF	80	5
c	1	10	DMF	115	72
d	1	10	1,4-Dioxane	Reflux	48
e	1	10	DMA	115	72
f	16	10	DMF	115	66

[a] NR = no reaction.

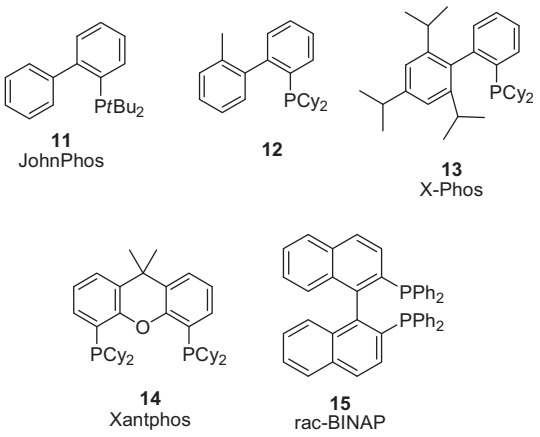
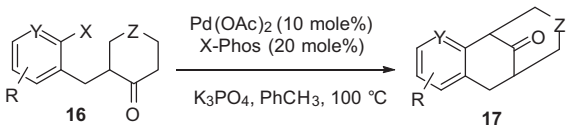
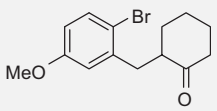
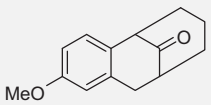
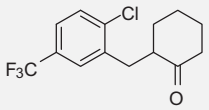
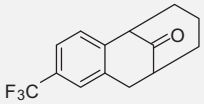
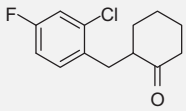
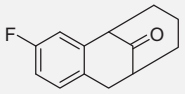
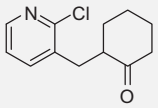
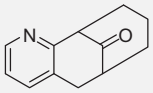
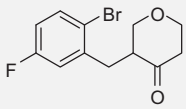
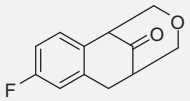
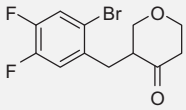
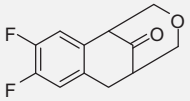
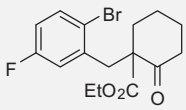
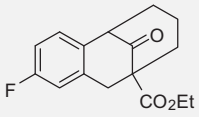


Figure 2. Phosphine ligands used in optimization studies.

Table 3
Scope of the intramolecular ketone α-arylation of 2-(2-halobenzyl)-cyclohexanones



Entry	Substrate	Product	Yield (%)
a			60
b			61
c			84
d			26
e			98
f			100
g			74

Since proteo-reductive elimination to form the des-bromo by-product **10** remained a significant issue, we investigated the addition of sterically hindered electron-rich phosphine ligands to potentially increase the rate of the desired C–C bond-forming reductive elimination event and decrease the rate of the proteo-reductive elimination event. Toward this end, we were encouraged by the reports of Buchwald and co-workers on the use of electron-rich phosphine ligands in intermolecular α-arylations of ketones.[9] Screening of several (Fig. 2) phosphine ligands **11**–**15** (entries n–r) with $Pd(OAc)_2$ and K_3PO_4 in toluene identified X-Phos **13** as the most successful ligand, yielding **9** in 84% yield with no detectable amount of the des-bromo by-product **10** (entry p). We believe that the success of the X-Phos **13** ligand is due to the highly sterically encumbered environment about the P atom, which significantly enhances the rate of the desired C–C bond reductive elimination event. The reaction conditions of X-Phos **13**/$Pd(OAc)_2$ and K_3PO_4 in toluene met our goal to identify more tractable reaction conditions for the conversion of **8** to **9**, and have proven to be scalable to >100 g scale. These conditions provided **9** as a racemic mixture of a single diastereomer. We were interested in developing an enantioselective version on this cyclization. However, initial efforts toward an enantioselective α-arylation of **8** were not successful, as the use of *rac*-BINAP **15** as a ligand resulted in no reaction (entry r). This precluded us from examining the separate BINAP enantiomers. However, it is possible that other chiral phosphine ligands may promote the cyclization of **8** in an enantioselective fashion.

Once optimal, reproducible, and scalable reaction conditions were identified, we examined the scope of these conditions with a variety of 2-(2-halobenzyl)-cyclohexanones (Table 3). Electron-rich substrates such as **16a** underwent facile cyclization to yield **17a** in 60% yield. Aryl chlorides were also useful cyclization substrates, as **16b** and **16c** afforded the corresponding cyclic products **17b** and **17c** in 61% and 84% yields, respectively. Heterocyclic chlorides were also tolerated, although the cyclization of **16d** led to product **17d** in a reduced 26% yield. Variation was also tolerated in the cyclohexanone portion, as the 4-oxo-cyclohexanone substrates **16e** and **16f** underwent cyclization to afford **17e** and **17f** in >98% yields. The 2,2-disubstituted cyclohexanone **16g** also underwent cyclization to yield **17g** in good yield. Substrates such as **17g** may also be useful to access enantiomerically pure tricyclo-[7.3.1.$0^{2,7}$]-trideca-2,4,6-trien-13-ones if the quaternary center in **16g** can be prepared in an enantioselective fashion. Alternatively, the carboxylate functional group could be derivatized as a suitable chiral auxiliary that might provide sufficient enolate facial selectivity.

2. General bench-scale synthetic procedure for the intramolecular α-arylation of 2-(2-halobenzyl)-cyclohexanones using $Pd(OAc)_2$/X-Phos

2.1. Synthesis of 5-fluoro-tricyclo-[7.3.1.$0^{2,7}$]-trideca-2,4,6-trien-13-one (9)

An oven-dried, 100 mL round-bottommed flask was cooled under Ar and charged with 140 mg (0.62 mmol) of $Pd(OAc)_2$, 592 mg (1.24 mmol) of X-Phos **13**, and 3.03 g (14.3 mmol) of anhydrous K_3PO_4. A solution of 1.77 g (6.21 mmol) of 2-(2-bromo-5-fluorobenzyl)-cyclohexanone **3** in 25 mL of anhydrous toluene was added, and the resulting suspension was heated to reflux for 18 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, filtered through Celite, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 10% EtOAc/hexanes) gave 1.067 g (84%) of **4** as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45–1.63 (m, 2H), 1.95–2.15 (m, 4H), 2.74–2.78 (m, 1H), 3.17 (d, J = 17.8 Hz, 1H), 3.43 (dd, J = 17.8, 7.2 Hz, 1H), 3.45–3.49 (m, 1H), 6.84–6.88 (m, 1H), 6.90–6.93 (m, 1H), 6.94 (dd, J = 12.0 Hz, 5.9 Hz, 1H); MS calcd for [$C_{13}H_{13}FO$+1]: 205.2. Found (APCI): 205.1 (M+1).

3. General large-scale synthetic procedure

3.1. Synthesis of 5-fluoro-tricyclo-[7.3.1.0^{2,7}]-trideca-2,4,6-trien-13-one (9)

A 5-L multi-neck round-bottommed flask equipped with a stir bar was charged with 575 g (2.06 mol) of 2-(2-bromo-5-fluorobenzyl)-cyclohexanone **3**, 85 g (0.178 mol) of X-Phos **13**, 990 g (4.65 mol) of anhydrous K_3PO_4, and 5.5 L of toluene. The mixture was degassed under vacuum and then treated with 42 g (0.19 mol) of $Pd(OAc)_2$. The reaction mixture was heated to reflux for 36–40 h until complete by TLC. After cooling to room temperature, the reaction mixture was filtered through Celite, washed with EtOAc, and concentrated to a dark orange oil. The crude material was purified by chromatography on silica gel, eluting with 97:3 cyclohexane/EtOAc. An impurity with slightly higher R_f than the product complicated the purification. The cleanest fractions were combined and concentrated to give 185 g of **4** (45% yield, 96.8% pure by GC). Concentration of impure fractions gave an additional 60 g of **4** that was 89% pure by GC for an overall yield of 59%.

In summary, we have demonstrated that use of the X-Phos ligand **13** in the Pd-catalyzed intramolecular ketone α-arylation of 2-(2-halobenzyl)-cyclohexanones results in an efficient, reproducible, and scalable synthesis of tricyclo-[7.3.1.0^{2,7}]-trideca-2,4,6-trien-13-ones. A variety of substitution patterns on the aryl halide and cyclohexanone portions are tolerated. Both aryl chlorides and bromides undergo facile reaction. This route has enabled the rapid investigation of structure–activity relationships about the tricyclic core ring structure. We believe that the optimization conditions detailed herein will be of interest to others investigating the intramolecular α-arylation of carbonyl compounds.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data for compounds **9** and **17a**–**g**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.085.

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