Tricyclic Indolines

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Palladium-Catalyzed γ-Arylation of β,γ-Unsaturated Ketones: Application to a One-Pot Synthesis of Tricyclic Indolines**

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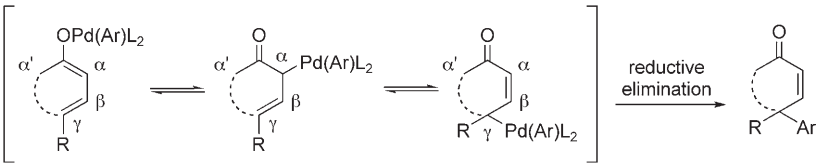
Extensive work has been carried out to develop the palladium-catalyzed α-arylation of ketones and related carbonyl functional groups,[1] providing a very simple and dependable route to α-aryl and α-vinyl ketones. However, less attention has been directed to the palladium-catalyzed arylation of dienolates,[2] which would allow for rapid construction of γ-aryl-α,β-unsaturated ketone motifs (Scheme 1) found in a number of natural products.[3] Many methods already exist to produce α-arylated or α-vinylated α,β-unsaturated ketones[4] from a variety of precursors, but the means to produce γ-aryl- or γ-vinyl-α,β-unsaturated ketones[2,5] are limited. Several factors contribute to the difficulty of developing such a process: 1) dienolates are less nucleophilic than enolates, 2) dienolates are more prone to self-condensation through Michael reactions, and 3) there is the potential for the generation of regioisomeric products.



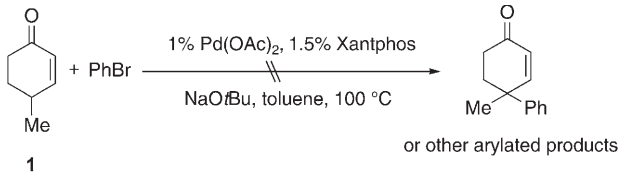
Scheme 1. Regioselective dienolate arylation.

A number of approaches have been developed to control the regioselectivity in the alkylation of α,β-unsaturated ketones and esters. For example, if α,β-unsaturated ketones or carboxylic acid derivatives are treated with an alkyl halide in the presence of alkali-metal bases such as KO*t*Bu[4a] or lithium diethylamide (LDE),[4b,c] alkylation occurs at the α-position preferentially over the γ- or α′-positions. The regioselectivity of this reaction may be reversed to favor γ-alkylation with the use of copper,[4d,e] germanium,[4f] tin,[4g] or zinc[4h,i] dienolates.

Building upon this concept, Yamamoto et al. reported that preformed tin dienolates will undergo cross-coupling at the γ-position with aryl bromides in the presence of [Pd-(PPh_3)$_4$] with high selectivity.[2a,b] However, low yields and the use of stoichiometric amounts of tin compounds preclude this method from being generally applicable. An alternative method for this transformation was published in 1998 by Miura and co-workers, demonstrating that α,β-unsaturated ketones and aldehydes react with aryl bromides under basic conditions selectively at the γ-position using a $Pd(OAc)_2$/PPh_3-based catalyst.[2c] However, no examples were described in which a quaternary carbon center was formed by a regioselective γ-arylation.

Herein, we show that with the proper choice of ligand and base, quaternary carbon centers can be formed by arylation or vinylation at the γ-position of β,γ-unsaturated ketones. We then apply this methodology to a convenient two-step, one-pot synthesis of ketoindolines that allows for the rapid construction of compounds that contain a polycyclic alkaloid framework.

We first sought to react 4-methylcyclohex-2-en-1-one (**1**) with bromobenzene using conditions established for the α-arylation of ketones[1b] using NaO*t*Bu as the base and a $Pd(OAc)_2$/Xantphos-based catalyst (Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene). This reaction was unsuccessful, however, resulting only in self-condensation of the ketone (Scheme 2).



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Scheme 2. Unsuccessful attempt to arylate α,β-unsaturated ketone **1**.

We then began screening reaction conditions with β,γ-unsaturated ketone **2**, since it was easier to prepare than **1**. We discovered that the use of a weak base such as Cs_2CO_3 was crucial to obtain any arylated product. We also found that the optimal ligands used for α-arylation, such as Xantphos (Table 1, entry 2) or binap (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Table 1, entry 8) gave poor yields when used

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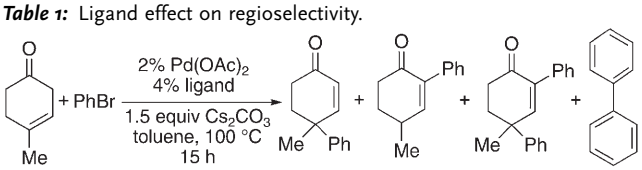
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

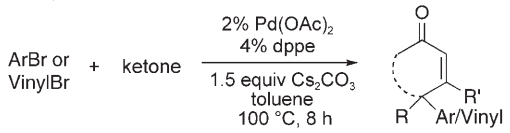
Table 1: Ligand effect on regioselectivity.

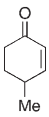
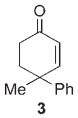
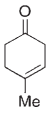
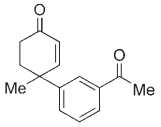
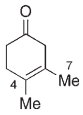
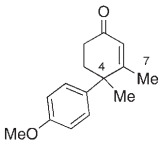
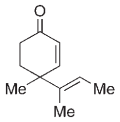
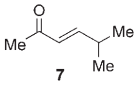
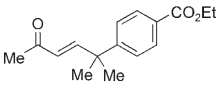
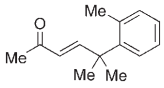


Entry	Ligand	Yield [%][a]			
		3	**4**	**5**	**6**
1	P(*o*-tol)$_3$	35	0	23	26
2	Xantphos	11	12	49	0
3	CyJohnPhos	41	7	17	14
4	Xphos	0	4	50	0
5	dppe	84	0	0	0
6	dppp	56	0	0	5
7	dppb	50	2	7	0
8	*rac*-binap	50	7	32	0
9	dppf	28	25	53	0
10	P(*t*Bu)$_3$·HBF$_4$	7	0	27	0

[a] Yields determined by GC using an internal standard of dodecane. CyJohnPhos = 2-(dicyclohexylphosphino)biphenyl, Xphos = 2-(dicyclohexylphosphino)-2′,4′,6′-tri-*iso*-propyl-1,1′-biphenyl, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, *o*-tol = *ortho*-tolyl.

Table 2: γ-Arylation of unsaturated ketones.[a]



Entry	Ketone	Product	Yield [%][b]
1		 **3**	70
2	 **2**	**3**	81
3	**2**		80
4			61
5	**2**		66[c]
6	 **7**		54[d]
7	**7**		70[d,e]

[a] The nature of the halide reagent can be deduced from the products. [b] Yields of isolated product are based on an average of two runs. [c] Reaction run at 110 °C in 3:1 dioxane/THF. [d] Greater than 98:2 ratio of *E*/*Z* isomers are formed. [e] Reaction run at 110 °C in dioxane using dppb as the ligand.

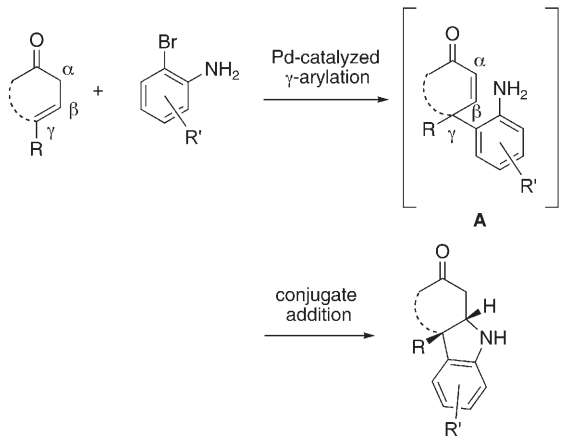
for γ-arylation, producing a mixture of γ-arylated (**3**), α-arylated (**4**), and doubly arylated (**5**) products. Arylation at the α′-position is never observed. Upon screening a variety of other ligands, we found that the use of a bidentate ligand with a narrow bite angle[6] is necessary to achieve high selectivity (Table 1, entries 5–7). The small diphosphine dppe was particularly effective, giving exclusively the γ-arylated product in 84% yield (Table 1, entry 5).

We do not yet understand the nature of the influence of ligand structure on the observed regioselectivity. We postulate that the selectivity reflects the relative rate of reductive elimination from the α- and γ-positions and is very sensitive to both the electronic and steric environment at the Pd center.

It is also noteworthy that β,γ-unsaturated ketones give higher yields than α,β-unsaturated ketones as substrates (Table 2, entries 1 and 2). This difference can likely be attributed to the greater acidity and lower tendency for self-condensation of β,γ-unsaturated ketones. The required β,γ-unsaturated cyclohexenones are conveniently prepared by a Birch reduction–hydrolysis sequence from the corresponding anisoles.[7]

Once reliable conditions to synthesize γ-arylated α,β-unsaturated ketones were established, the scope of the process was examined (Table 2). The reaction can be performed in the presence of a methyl ketone substituent with no arylation of this ketone (Table 2, entry 3). This example clearly demonstrates that the conditions needed for the γ-arylation of ketones are orthogonal to those for α-arylation. Entry 4 (Table 2) shows that selective arylation at carbon 4 may be achieved; in contrast, if the isomeric α,β-unsaturated ketone 3,4-dimethylcyclohex-2-en-1-one, is used, a mixture of products is obtained owing to competitive arylation at carbons 4 and 7. This reaction also works well with vinyl bromides under slightly modified conditions, producing γ-vinyl-α,β-unsaturated ketones (Table 2, entry 5). γ-Arylation of acyclic α,β-unsaturated ketone **7** proceeds in moderate to good yield (Table 2, entries 6 and 7). In these cases, the commercially available ketone **7** is used, as it gives similar yields to the isomeric β,γ-unsaturated ketone. The reaction proved to be sensitive to steric hindrance, as the reaction of an aryl bromide possessing an *ortho*-methyl group under the standard conditions gives a mixture of α-, γ-, and doubly arylated products. However, changing the ligand to dppb and the solvent to dioxane provides the γ-arylated isomer as the exclusive product in 70% yield (Table 2, entry 7).

With an efficient procedure for the γ-arylation of ketones in hand, we wondered whether it would be possible to combine a β,γ-unsaturated ketone with an *ortho*-bromoaniline to provide intermediate **A** (Scheme 3). We reasoned that subsequent intramolecular conjugate addition would produce the indoline shown in Scheme 3. Methods to prepare cyclo-



Scheme 3. Proposed sequence to generate ketoindolines.

hexanone-fused indolines have been reported[8] but either involve multiple steps or start with an indole. Heterocycles of this type are of interest, as they are precursors in the synthesis of a number of the *Aspidosperma* alkaloids including vindoline,[9] aspidophytine,[10] and the "Büchi ketone" intermediate.[8a]

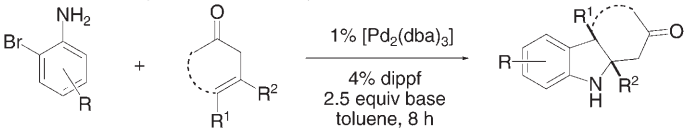
Our initial attempts to carry out the transformation shown in Scheme 3 quickly revealed that the choice of the ligand was again critical; the use of dppe gave none of the desired product. Of the ligands tested, only 1,1′-bis(di-*iso*-propylphosphino)ferrocene (dippf) gave consistently good yields. When coupling *ortho*-bromoaniline derivatives, α-arylation was never observed, and the two-step domino process proceeded with complete regioselectivity and *cis*-diastereoselectivity. For this process, it was found in all instances that α,β-unsaturated ketones gave significantly lower yields than the isomeric β,γ-unsaturated ketones.

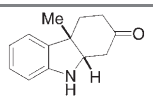
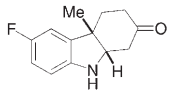
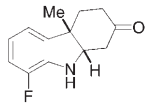
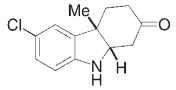
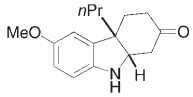
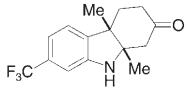
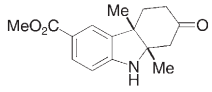
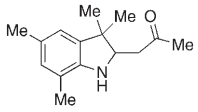
We initially suspected that an aniline derivative bearing a protected amino group would provide better results. However, N-protected 2-bromoaniline derivatives proved to be very poor substrates in the arylation reaction, and only the use of 2-bromoaniline gave satisfactory yields.

As shown in Table 3, the substrate scope for the indoline-forming process is quite broad, and the reaction demonstrates a high level of functional-group tolerance. Electron-rich and electron-neutral bromoanilines can be transformed in the presence of Cs_2CO_3 at 100 °C (Table 3, entries 1, 5, and 8). However, electron-poor bromoanilines necessitate the use of K_2CO_3 at 110 °C for their reactions to reach full conversion (Table 3, entries 2–4, 6, and 7). Notably, the indolines produced may be acyclic (Table 3, entry 8), mono- (Table 3, entries 1–5) or disubstituted (Table 3, entries 6 and 7), at the 2- and 3-positions. Unfortunately, to date, all attempts to perform this reaction with either α,β- or β,γ-unsaturated cyclopentenones have been unsuccessful.

We next turned our attention to developing an asymmetric version of this indoline synthesis. Successful protocols have been developed for both nickel-catalyzed[11a] and palladium-catalyzed[11b–d] asymmetric α-arylation of ketones. Given these precedents we were optimistic that a chiral ligand could be found that would impart high facial selectivity to the ketone. An extensive ligand screening revealed that an enantiomeric excess of up to 92% could be achieved using DTBM-Segphos as the supporting ligand (Table 4). The absolute stereochemistry of indoline **8** was established by

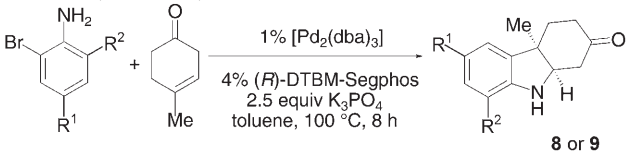
Table 3: One-pot ketoindoline synthesis.[a]



Entry	Base	*T* [°C]	Product	Yield [%][b]
1	Cs_2CO_3	100		81
2	K_2CO_3	110		63
3	K_2CO_3	110		60
4	K_2CO_3	110		64
5	Cs_2CO_3	100		66
6	K_2CO_3	110		50
7	K_2CO_3	110		69
8	Cs_2CO_3	100		70

[a] dba = *trans*,*trans*-dibenzylideneacetone. [b] Yields of isolated product are based on an average of two runs.

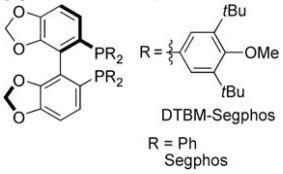
Table 4: Asymmetric synthesis of indolines.



8 or **9**

Entry	R^1	R^2	Yield [%][a]	*ee* [%][b]
1 (**8**)	Me	Me	50	90
2 (**9**)	OMe	H	32	92

[a] Yields of isolated product are based on an average of two runs. [b] Determined by chiral HPLC with an OJ column.



single crystal X-ray crystallography and is shown in Table 4.[12] Of importance is that the *t*Bu groups on the P-bound phenyl rings are critical for this selectivity, as the use of Segphos only gives 41% *ee*. To achieve higher yields, the racemic protocol was slightly modified by switching the Pd source to $Pd(OAc)_2$ and the base to K_3PO_4, but to date, conditions could not be found to give yields above 50%. Efforts to improve and generalize this process are ongoing.

In summary, we have developed a method for the selective γ-arylation or vinylation of α,β- or β,γ-unsaturated ketones to generate quaternary carbon centers. We have applied this method to a two-step, one-pot indoline synthesis with 2-bromoanilines as coupling partners. We have also made initial progress in the development of an asymmetric version of this reaction. Further work investigating the origin of ligand effects on the regioselectivity of arylation and the extension of the method to the synthesis of additional classes of heterocycles is currently underway.

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Keywords: γ-arylation · asymmetric catalysis · domino reactions · indolines · palladium

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[12] CCDC-662975 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

