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Facile and General Synthesis of Quaternary 3-Aminooxindoles

Stephen P. Marsden,*,† Emma L. Watson,† and Steven A. Raw‡

School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K., and AstraZeneca Process R&D, Charter Way, Silk Road Business Park, Macclesfield SK10 2NA, U.K.

s.p.marsden@leeds.ac.uk

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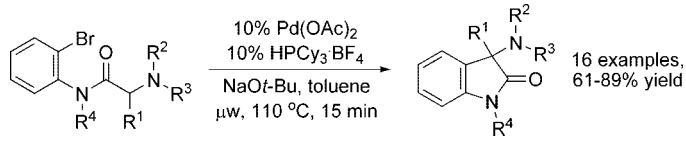
ABSTRACT



A novel approach to the valuable quaternary 3-aminooxindole skeleton is reported on the basis of intramolecular arylation of enolates of substituted amino acids. The reaction tolerates dialkyl- and arylalkylamines as well as a range of carbon substituents (primary and secondary alkyl, aryl). The cyclization of *N*-indolyl-substituted substrates is accompanied by direct C−H arylation of the indole, leading to indolo-fused benzodiazepines.

3,3-Disubstituted oxindoles constitute a valuable class of biologically active molecules. Among these structures, several quaternary 3-aminooxindoles have been promoted as pharmaceutical candidates, including the potent gastrin/CCK-B receptor antagonist AG-041R (**1**)[1] and the vasopressin VIb receptor antagonist SSR-149415 (**2**)[2] (Figure 1). Moreover, several members of the indole alkaloid family of natural products contain skeleta that could potentially be accessed synthetically via 3-aminooxindoles. Pertinent examples include the 3*H*-indole skeleton of the chartellines (e.g., chartelline C, **3**)[3] and the hexahydropyrroloindole skeleton of the immunosuppressant psychotrimine (**4**).[4]

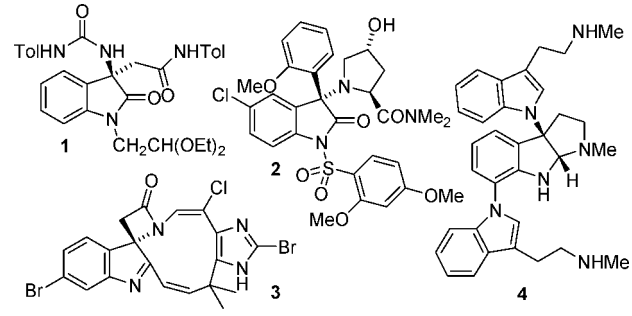


Figure 1. Bioactive quaternary aminooxindoles and indolines.

Quaternary 3-aminooxindoles have previously been synthesized by a variety of methods, including alkylation of 3-aminooxindoles,[5] substitution of 3-chlorooxindoles by amines,[6] Mannich reactions[7] and Staudinger [2 + 2] cycloadditions[8] of isatin imines, [3 + 2] cycloadditions of isatin-derived azomethine ylides,[9] radical addition[10] and

† University of Leeds.
‡ AstraZeneca Process R&D.

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cyclization reactions,[11] reductive cyclization of S_NAr-derived nitroarylglycines,[12] and aziridination of 3-methylideneoxindoles.[13] However, these strategies lack generality in that a given protocol cannot be commonly applied to diverse C3-substituents (alkyl or aryl carbon substituents; alkyl or aryl amine substituents) or can only provide access to spirocyclic derivatives.[8,9,13] The development of a novel method for the synthesis of 3-aminooxindoles that enables complete control of the C3-substituents would therefore be of significant value. We report herein the first use of palladium-catalyzed enolate arylation to achieve this goal.

The synthesis of oxindoles (including 3,3-disubstituted variants) by palladium-catalyzed intramolecular arylation of anilide enolates developed by Hartwig[14] has received some attention,[15] and asymmetric variants[14b,16] of the reaction with usable (>90% ee) levels of enantioselectivity were recently reported by Kündig.[16d]

The application of this reaction to the synthesis of 3-aminooxindoles is very appealing since the requisite anilide substrates **5** can be readily accessed from commercially available α-haloalkanoyl halides or amino acid methyl esters, leading to diverse substitution in the product oxindoles **6** (Figure 2). The tolerance of the intramolecular enolate

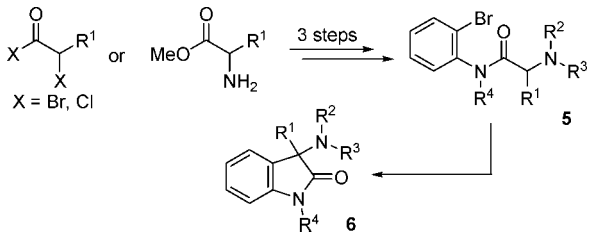
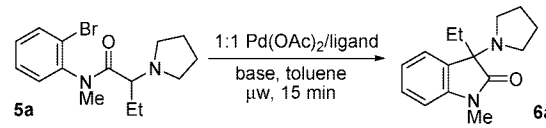


Figure 2. Enolate arylation strategy for the synthesis of quaternary 3-aminooxindoles.

arylation to heteroatom substituents has not been widely probed, however; there has been only a single application to a C3-oxygenated oxindole,[14b] and at the outset of this work there were no examples of the synthesis of nitrogen-substituted oxindoles. Given the potentially strong metal−ligand interaction between an amine and the palladium catalyst, the innocent behavior of the nitrogen substituent in the reaction could not be guaranteed. We therefore set out to establish reaction conditions for the efficient cyclization of substrate **5a**, containing a basic pyrrolidinyl group as the nitrogen substituent (Table 1).

Table 1. Optimization of Arylation Reaction Conditions



entry	base	ligand	% cat.	T (°C)	yield[a] (%)
1	NaO-*t*-Bu	$HPCy_3{\cdot}BF_4$	10	100[b]	10[c]
2	NaO-*t*-Bu	$HPCy_3{\cdot}BF_4$	10	110[b]	12
3	NaO-*t*-Bu	$HPCy_3{\cdot}BF_4$	10	110	76
4	NaO-*t*-Bu[d]	$HPCy_3{\cdot}BF_4$	10	110	61
5	LHMDS	$HPCy_3{\cdot}BF_4$	10	110	0
6	Cs_2CO_3	$HPCy_3{\cdot}BF_4$	10	110	0
7	NaO-*t*-Bu	DavePhos	10	110	28
8	NaO-*t*-Bu	PPh_3[e]	10	110	8
9	NaO-*t*-Bu	$HPCy_3{\cdot}BF_4$	5	110	33
10	NaO-*t*-Bu	$HPCy_3{\cdot}BF_4$	10	130	70

[a] Isolated yield. [b] Conventional heating (oil bath). [c] Reaction carried out in dioxane. [d] 2 equiv of base used. [e] $Pd(PPh_3)_4$ used as palladium/ligand source.

Initial reactions were carried out (using conditions close to Hartwig's original report[14]) under conventional heating (oil bath) in dioxane and toluene, with both systems giving poor conversions (entries 1 and 2). In the reaction in dioxane, some hydrodebromination of the starting material was also observed, so toluene became the solvent of choice. On moving to microwave-mediated heating (fixed temperature) in a sealed vessel, complete consumption of the starting material was observed and a 76% isolated yield of aminooxindole obtained (entry 3). Altering the stoichiometry or nature of the base did not improve the process (entries 4−6), and other phosphine ligands were less effective than tricyclohexylphosphine (entries 7 and 8).

With optimized conditions identified, we next examined the substrate scope of the reaction with respect to both the nitrogen and carbon enolate substituents (Table 2).

The reaction shows remarkable tolerance to a range of substituents with markedly different steric and electronic properties. We first examined the influence of the nitrogen substituent, keeping the (ethyl) carbon substituent constant (entries 1−8). The reaction works equally well with cyclic and acyclic dialkylamine substituents, and pleasingly, aromatic amines are also tolerated (entries 5 and 6). Cyclization of the protected prolinol-containing substrate **5h** was successful but with no evidence for any stereocontrol in the cyclization reaction from the existing asymmetric center (entry 7). More readily deprotected *N*-Bn oxindoles can also be prepared (entry 8). With respect to carbon substituents, β-branched primary and secondary alkyl substituents have little if any deleterious effect on yield (entries 9−11), while substrates with aromatic substituents also cyclize effectively (entries 12−14).

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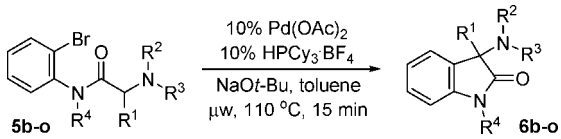
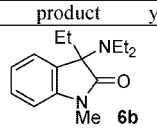
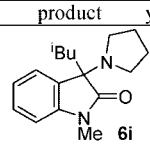
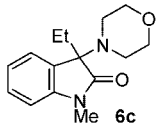
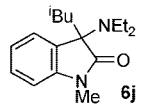
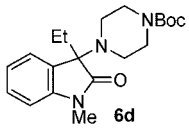
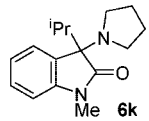
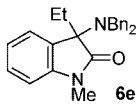
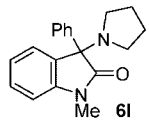
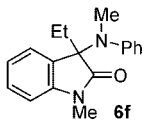
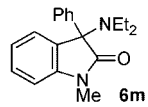
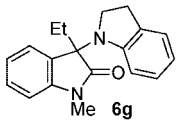
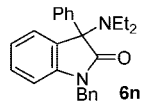
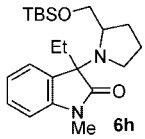
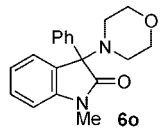
Table 2. Substrate Scope of Enolate Arylation Approach to Quaternary Aminooxindoles

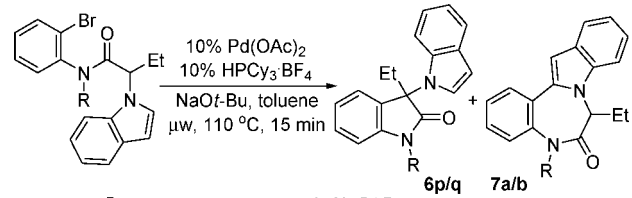


entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **6b**	89	8	 **6i**	72
2	 **6c**	84	9	 **6j**	66
3	 **6d**	86	10	 **6k**	78
4	 **6e**	80	11	 **6l**	66
5	 **6f**	83	12	 **6m**	73
6	 **6g**	64	13	 **6n**	63
7	 **6h**	61[b]	14	 **6o**	70

[a] Isolated yield. [b] 1:1 mixture of diastereoisomers.

A further interesting class of substrates we wished to examine was the *N*-indolyl-substituted substrates **5p**,**q**. These are of interest since the transformation could serve as an approach to the 3-(*N*-indolyl)-substituted indole alkaloids such as the kapakahines,[17] the chetomin/chetoseminudin/chaetococcin family,[18] and psychotrimine (**4**),[4] the latter being the only subject to date of a published synthetic approach.[19] However, a survey of the literature revealed limited examples of the enolate chemistry of α-(*N*-indolyl)carboxyl substrates[20] and only a sole example leading to a quaternary center,[20c] raising concerns about the viability of these species in the arylation process. In the event, under our standard conditions, compound **5p** underwent efficient arylation to deliver the desired arylation product **6p** in 65% yield (Scheme 1). This compound was accompanied by a small amount (3%) of what appeared to be the indolo-fused benzodiazepinone **7a**, the product of a competing direct intramolecular C2-arylation of the indole.[21] The identity of the compound and its likely mechanism of formation were established by repeating the reaction under identical conditions, but utilizing only sufficient base to liberate the free phosphine ligand. In the absence of any base to promote enolate formation, compound **7** was the sole product of the reaction, isolated in a modest 26% yield. Interestingly, compounds with this heterocyclic skeleton have been shown to have interesting activity against hepatitis C virus,[22] and further optimization of this reaction may provide a useful approach to this system. In this regard, when the *N*-benzyl-protected substrate **5q** was treated under the standard enolate arylation conditions, the reaction afforded only the benzodiazepinone **7b** in an unoptimized 60% yield. This suggests that the balance between enolate and direct indole arylation can be engineered by modification of the substrate structure as well as the reaction conditions.

Scheme 1. Arylation Reactions of Indole-Containing Substrates



			6p/q	7a/b
5p	R = Me	3 equiv NaO*t*-Bu:	65%	3%
		0.1 equiv NaO*t*-Bu:	0%	26%
5q	R = Bn	3 equiv NaO*t*-Bu:	0%	60%

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In summary, we have demonstrated that palladium-catalyzed enolate arylation chemistry is tolerant of a wide range of amine substituents on the enolate, leading to an efficient and novel approach to the biologically interesting 3-aminooxindole structure. The substrates are readily prepared from widely available amino acid or α-halocarbonyl starting materials, greatly enhancing the synthetic potential of the method. The development of asymmetric variants and synthetic applications of the method are under evaluation, as are further studies of the formation of benzodiazepinones **7** by direct arylation, and the results will be reported in due course.

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Supporting Information Available: Compound characterization data and spectra for compounds **5a**−**q**, **6a**−**p**, and **7a/b**, together with standard experimental protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

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