Allylations

Palladium-Catalyzed Asymmetric Allylation of Prochiral Nucleophiles: Synthesis of 3-Allyl-3-Aryl Oxindoles**

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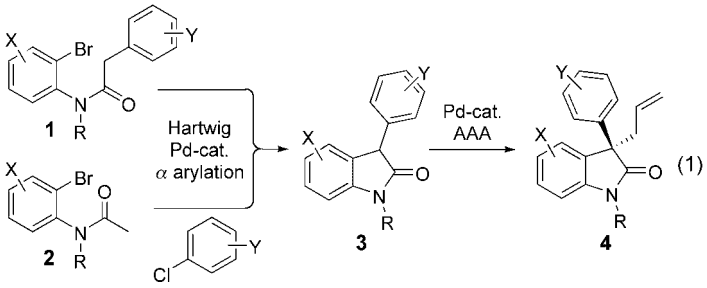
The generation of quaternary centers with control of absolute stereochemistry represents a fundamental challenge in synthetic organic chemistry.[1] In this area, we have examined the ability of asymmetric allylic alkylation (AAA) to control stereochemistry at prochiral nucleophiles, a particularly daunting challenge given its direct attack at the face of the allyl fragment opposite to that bound to the metal. Our success with a few classes of nucleophiles exemplified by β-ketoesters,[2] ketones,[3] among others,[4–6] encouraged us to examine new classes of nucleophiles of particular significance such as lactam enolates.

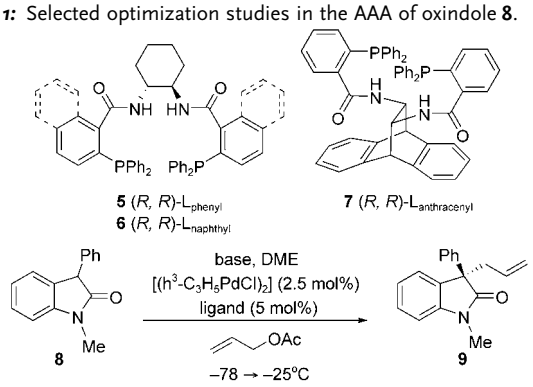
The 3-alkyl-3-aryl oxindole structural motif is a prominent feature in a number of biologically active natural products, for example, diazonamide A[7] and leptosin D,[8] as well as several pharmaceutically active compounds.[9] In spite of the importance of this structural motif, few general methods exist for its construction. Aside from the elegant asymmetric intramolecular Heck reaction developed by Overman and co-workers,[10] only scattered examples based on Pd-catalyzed α arylation[11] and asymmetric acyl transfer have been reported.[12] Pd-catalyzed AAA represents a conceptually novel and flexible approach to this important structural class, especially when combined with the powerful Pd-catalyzed α-arylation protocols for the synthesis of 3-aryl oxindoles developed by Hartwig and co-workers.[11,13] When used in concert, these processes would readily give access to structurally complex oxindoles endowed with a quaternary stereocenter from simple and readily available starting materials [Eq (1)]. Herein we report the successful development of this strategy.

Our studies commenced with a comprehensive matrix screen of bases in the presence of our standard set of ligands **5**–**7** in the Pd-catalyzed AAA reaction of oxindole **8** to form **9** (Table 1).[14] These experiments revealed large variations in yield and enantioselectivity, for example, the use of potassium carbonate in conjunction with ligands **5**–**7** showed a dramatic increase in both yield and *ee* values (Table 1, entries 1–3) relative to other counterions (results not shown). Weaker bases showed better compatibility with this reaction (Table 1, entries 4 and 5). Interestingly, 10 mol% KF gave essentially identical results to the stoichiometric reaction (Table 1, entries 5 and 6). This trend was also observed when nonmetal bases such as Et_3N (Table 1, entries 7 and 8) were used. When BSA was utilized, a spectacular increase in the *ee* value by 36% (from 40 to 76% *ee*) was observed when the base loading was lowered from 1 to 0.1 equivalent (Table 1, entries 9 and 10).



(1)

Table 1: Selected optimization studies in the AAA of oxindole **8**.



Entry	Ligand	Base (equiv)	Yield [%][a]	*ee* [%][b]
1	**5**	K_2CO_3 (1.1)	68	19
2	**6**	K_2CO_3 (1.1)	81	28
3	**7**	K_2CO_3 (1.1)	83	56
4	**7**	AcOK (1.1)	92	47
5	**7**	KF (1.1)	86	64
6	**7**	KF (0.1)	84	65
7	**7**	Et_3N (1.1)	66	73
8	**7**	Et_3N (0.1)	66	78
9	**7**	BSA[c] (1.1)	91	40
10	**7**	BSA[c] (0.1)	59	76

[a] Yield of isolated product after chromatography. In all cases, the yields based on recovered starting material are nearly quantitative (>98%). [b] Determined by chiral HPLC. [c] BSA = *N*,*O*-bis(trimethylsilyl)acetamide.

These observations combined with the proficiency of AcOK in this reaction suggested that the addition of only a catalytic amount of base was necessary to initiate the enolization, as ionization of allyl acetate maintained the catalytic concentration of base. However, either the enolate or enol may function as the nucleophile. As oxindoles tautomerize to hydroxyindoles, it seemed reasonable to probe whether it was in fact the latter that acted as the

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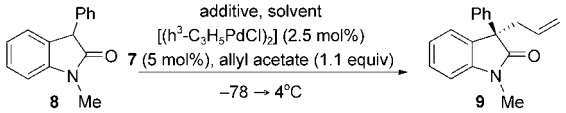
[**] We thank the National Science Foundation and the Institute of General Medical Sciences of the NIH (GM 13598) for their generous support of our programs and GlaxoSmithKline Research and Development (M.U.F.) for partial postdoctoral fellowship support.

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

  DOI: 10.1002/ange.200460335

nucleophile. In this case, the reaction should proceed without any external base. It was expected that the rate of tautomerization, and thus the rate of reaction, would be influenced by the polarity of the solvent (Table 2).

Table 2: Selected additive effects in the AAA of oxindole **8**.



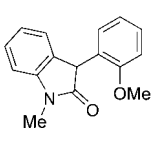
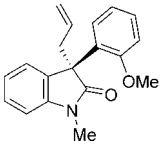
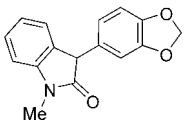
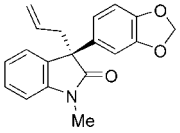
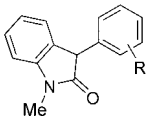
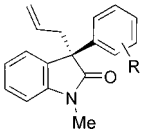
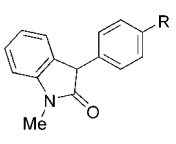
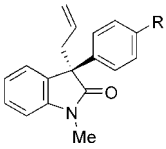
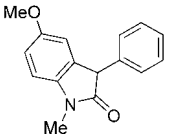
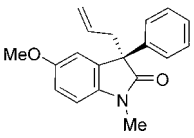
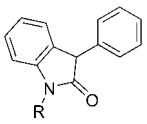
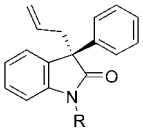
Entry	Solvent	*t* [h]	Yield [%][a]	*ee* [%][b]
1	DME	2	95	61
2	THF	2	75	72
3	CH_2Cl_2	12	31	61
4	PhMe	12	72	78
5[c]	PhMe	12	93	81

[a] Yield of isolated product after chromatography. In all cases, the yields based on recovered staring material are quantitative. [b] Determined by chiral HPLC. [c] *t*BuOH (4 equiv) was used as an additive in this reaction.

In accord with our predictions, the reaction proceeded when carried out in DME (1,2-dimethoxyethane) in the absence of any additives. The reaction was completed in 2 h at 4 °C and afforded **9** in excellent yield with 61 % *ee* (Table 2, entry 1). The reactions in THF occurred with higher enantioselectivity than the reactions in DME (Table 2, entry 2). Further optimization with respect to solvent showed that toluene allowed the highest enantioselectivity, albeit in lower yield (Table 2, entry 4). Reasoning that the oxindole–hydroxindole tautomerization would be significantly faster in hydroxylic media, we next examined the effect of various polar additives in their ability to promote the key tautomerization. After much experimentation, we found that the addition of 4 equivalents of *t*BuOH was optimal and provided the desired product **9** in 93 % yield with 81 % *ee* (Table 2, entry 5).[15] Notably, the yields based on returned starting material are always nearly quantitative, which serves as a testament to the extraordinary selectivity of this reaction. In summary, the use of *t*BuOH (4 equiv), $[(\eta^3\text{-}C_3H_5PdCl)_2]$ (2.5 mol %), and **7** (5 mol %) in toluene at 4 °C under neutral conditions became our standard reaction conditions for the synthesis of 3-aryl oxindoles.

With the optimized procedure established, we sought to examine the scope of the reaction. Thus a number of different aryl oxindoles were prepared and subjected to the standard conditions (Table 3).[16] Significant structural variation in the oxindole system can be accommodated in this reaction.[17] For example, an *ortho*-methoxy group is tolerated (Table 3, entry 1) and the sterically demanding product is obtained in good yield (72 %) with excellent enantioselectivity (97 % *ee*). Otherwise, the method is compatible with electron-rich (Table 3, entries 2–5 and 7) and electron-poor (Table 3, entry 6) aryl groups as well as aryl chloride substituents (Table 3, entry 8). The oxindole core may also be modified. Thus, both the benzo moiety (Table 3, entry 9) and the N-protecting group may be changed as well (Table 3, entries 10–14), for example, the trimethylsilylmethyl group (TMSM) can

Table 3: Scope of Pd-catalyzed AAA of 3-aryl oxindoles.

Entry	Substrate	Product	R	Yield [%][a]	*ee* [%][b]
1				72	97
2				68	79
3			*p*-Me	75	80
4			*m*-Me	96	77
5			*o*-Me	75	70
6			F	73	75
7			Ph	90	73
8			Cl	81	70
9				83	74
10			Me	93	81
11			TMSM[c]	76	80
12			Bn	75	70
13			SEM	81	68
14			MOM	96	66

[a] Yield of isolated product after chromatography. [b] Determined by chiral HPLC analysis, see Supporting Information for details. [c] TMSM = trimethylsilylmethyl.

be used (Table 3, entry 11). This group is interesting owing to the known propensity of such substrates to undergo dipolar cycloadditions,[18] and as such should give access to structurally diverse scaffolds. Other protecting groups may be incorporated, although at a slight detriment to the enantioselectivity. The lower *ee* values attained are intriguing: In the case of aromatic protecting groups (Table 3, entry 12), the lower enantioselectivity may be due to favorable interactions with the phenylphosphino moiety of the ligands which alter the approach of the nucleophile. MOM and SEM aminals (Table 3, entries 13–14) are likely to form stable hydrogen-bonded chelates that confer higher steric demands on the hydroxyindole nucleophile. Simple substituents (e.g. TMSM) may place their sterically demanding groups "outside" the chiral pocket, thereby allowing an ideal approach of the nucleophile to the Pd–allyl complex.

In summary, we have developed an enantioselective palladium-catalyzed AAA reaction for the synthesis of 3-alkyl-3-aryl oxindoles. The salient features of this approach

are: 1) extraordinarily mild reaction conditions, 2) good to excellent enantioselectivity in the generation of sterically congested quaternary stereocenters, 3) broad substrate scope, and 4) enantioselective access to important structural motifs from readily available and cheap starting material through two Pd-catalyzed processes.

Received: April 15, 2004
Revised: June 1, 2004

Keywords: allylation · asymmetric synthesis · heterocycles · homogenous catalysis · palladium

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[14] The depicted configuration is based on the absolute stereochemistry of products derived from the Pd-catalyzed AAA of the closely related 3-alkyl oxindoles, which were converted into known compounds: B. M. Trost, M. U. Frederiksen, unpublished results.
[15] The rate of tautomerization does not seem to be influenced by the addition of *t*BuOH alone, as preliminary ^{1}H NMR spectroscopic analyses of a solution of **8** in [D_8]toluene in the presence or absence of *t*BuOD do not differ appreciably. The addition of tetrabutylammonium acetate (5 mol%) shows significant exchange, whereas catalytic amounts of tetrabutylammonium chloride does not. We attribute this to a general acid–general base catalyzed enolization effected by *t*BuOH in combination with the acetate anion generated in situ.
[16] 3-Aryl oxindoles were prepared by α arylation; see Supporting Information for details.
[17] Despite the efficiency of this process, we have so far been unable to expand the scope with respect to other electrophiles.
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