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Asymmetric Decarboxylative Allylation of Oxindoles

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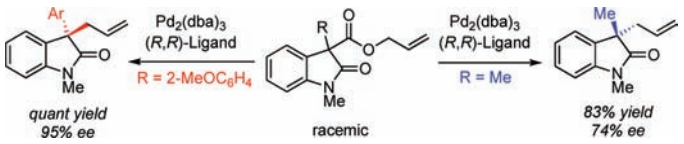
ABSTRACT



An asymmetric decarboxylative palladium-catalyzed allylation of alkyl- and aryl-substituted oxindoles has been developed, enabling the installation of an all-carbon quaternary chiral center at the oxindole 3-position in excellent yields and good to excellent enantioselectivity. An intriguing substrate-dependent reversal in stereoselectivity has been observed, whereby the size of the substituent determines the facial selectivity in the allylation step.

The oxindole structural motif is present in a large class of both bioactive naturally occurring alkaloids and synthetic analogs of medicinal value.[1] Bioactive oxindoles frequently contain a quaternary stereogenic center at the 3-position,[2] and a variety of catalytic asymmetric methods for constructing the tetra-substituted carbon center by means of metal- and organo-catalysis have been developed over the years.[3] Following the original report by Trost et al. of a catalytic asymmetric allylic alkylation[4] of ketone enolates,[5] methods for the installation of a quaternary carbon center in the 3-position of oxindoles by way of either palladium[6] or molybdenum[7] catalysis have been reported. However, no one method is applicable to both alkyl- and aryl-substituted oxindoles. In addition, either the use of stoichiometric amounts of base for enolate generation or elevated temperature is required for the reaction to proceed efficiently.

In order to establish reaction conditions which would not necessitate the use of a base and be suitable for a broader range of oxindole substrates, we aimed to exploit the utility of the Tsuji–Trost decarboxylative allyl group transfer process as a stereoselective entry to 3,3-disubstituted oxindoles.[8] Although the decarboxylative palladium-mediated allyl transfer processes with enolates as nucleophiles have now matured into a robust asymmetric transformation,[9] with major contributions from the groups of Tunge,[10] Trost,[11] and Stoltz,[12] among others,[13] an asymmetric variant for the installation of a quaternary center at the oxindole 3-position has not been reported to

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(2) For reviews concerning synthesis of substituted oxindoles, see: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) Ramon, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (f) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (g) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

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(8) (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793. (c) Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1983**, 1325. (d) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. For reviews, see: (e) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715. (f) Pan, Y.; Tan, C.-H. *Synthesis* **2011**, 2044.

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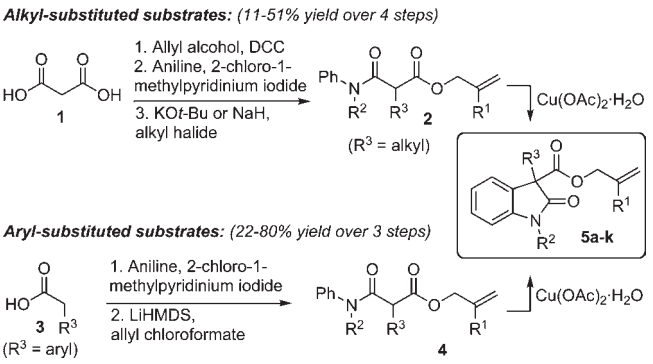
date. We therefore set out to prepare suitable oxindoles to test this idea.

Scheme 1. Substrate Synthesis

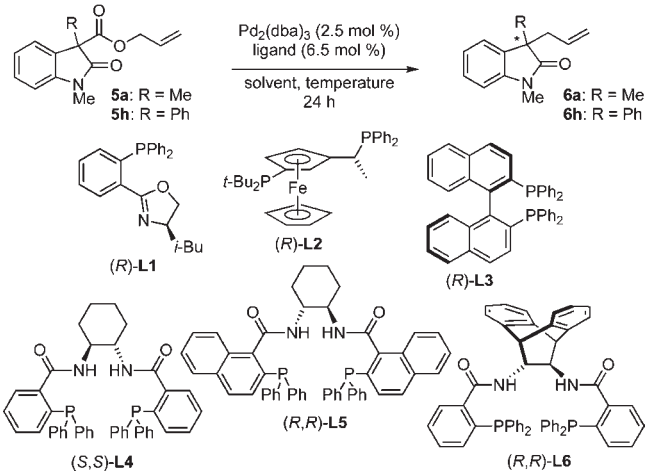


All oxindole substrates in this study were readily accessible (Scheme 1). More specifically, monoesterification of malonic acid (**1**), followed by anilide formation and introduction of an alkyl substituent, afforded linear intermediates of type **2**. Similarly, amide bond formation from phenylacetic acid **3** and allyloxycarbonylation generated aryl-substituted linear precursors **4**. Both **2** and **4** were then readily transformed to the cyclic oxindole core **5** by means of the recently developed copper(II)-mediated radical cyclization via a direct C−H, Ar−H coupling.[14]

With allyl esters **5** in hand, we began our decarboxylative allyl transfer studies by evaluating the effect of chiral ligands, solvents, and temperature on the reaction with oxindoles **5a** and **5h** as test substrates (Table 1).

In this optimization study, the reactivity of the methyl-substituted substrate **5a** was explored first and reactions were run in THF at room temperature for 24 h, with $Pd_2(dba)_3$ as the source of palladium(0) in the presence of a chiral ligand. Although Helmchen PHOX ligands of type **L1**[15] have been shown previously to mediate decarboxylative allyl transfer with ketone substrates with high enantioselectivity,[12] **L1** was not selective in this case, affording an essentially racemic product, albeit in good yield (Table 1, entry 1). The use of JOSIPHOS (**L2**) and BINAP (**L3**) only marginally improved the enantioselectivity (Table 1, entries 2 and 3). Interestingly, Trost ligands **L4** and **L5** led to not only poor selectivity but also a dramatic drop in conversion (Table 1, entries 4 and 5). In contrast, with the commercially available anthracenyl **L6** as a ligand, which had previously been successfully utilized by Trost,[6a] the reactivity was restored to provide **6a** in an improved 73% yield and 46% ee (Table 1, entry 6). At this point, a thorough solvent screen had allowed us to establish that comparable results can also be obtained with DME as the solvent (Table 1, entry 7). Finally, a lower reaction temperature with both THF and DME resulted in a significant improvement in selectivity (Table 1, entries 8 and 9, 83% yield and 74% ee of **6a** in DME), although further reduction in reaction temperature in DME halted the reaction altogether (Table 1, entry 10). Similar optimization indicated that, in the case of aryl-substituted

Table 1. Optimization of Reaction Conditions



entry	R	solvent	temp (°C)	ligand	yield (%)[a]	ee (%)[b]
1	Me	THF	rt	(*R*)-**L1**	82	4
2	Me	THF	rt	(*R*)-**L2**	92	−6
3	Me	THF	rt	(*R*)-**L3**	95	−14
4	Me	THF	rt	(*S,S*)-**L4**	32	4
5	Me	THF	rt	(*R,R*)-**L5**	10	−12
6	Me	THF	rt	(*R,R*)-**L6**	73	46
7	Me	DME	rt	(*R,R*)-**L6**	92	52
8	**Me**	**THF**	**−40**	(*R,R*)-**L6**	**85**	**57**
9	**Me**	**DME**	**−25**	(*R,R*)-**L6**	**83**	**74**
10	Me	DME	−40	(*R,R*)-**L6**	0	–
11	**Ph**	**toluene**	**−25**	(*R,R*)-**L6**	**99**	**79**

[a] Isolated yield. [b] Determined by chiral HPLC.

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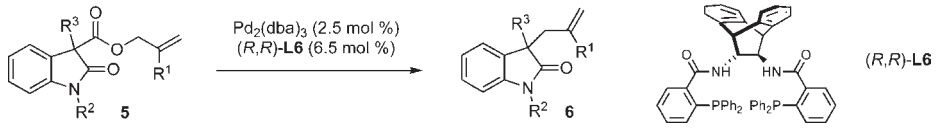
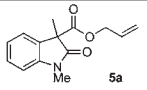
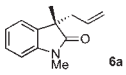
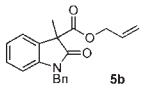
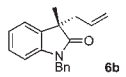
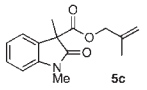
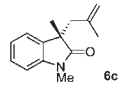
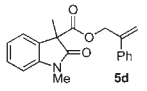
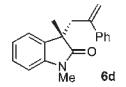
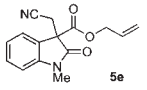
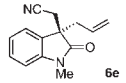
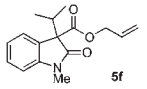
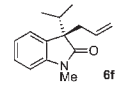
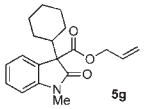
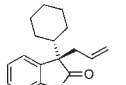
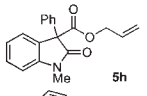
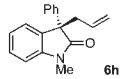
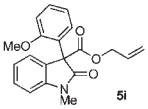
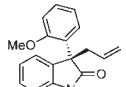
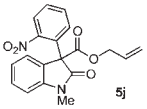
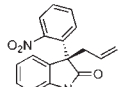
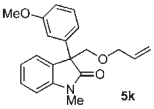
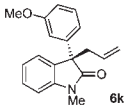
(14) (a) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446. (b) Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, 934. (c) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. (d) Jia, Y. X.; Kundig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636.

(15) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3047.

Table 2. Investigation of Substrate Scope



entry	substrate	product[a]	A-value, (kcal/mol)[b]	conditions	yield, (%)[c]	ee, (%)[d]
1	 5a	 6a	1.74	**DME, –25 °C, 24 h**	**83**	**74**
				THF, –40 °C, 24 h	85	57
2	 5b	 6b	1.74	**DME, –25 °C, 24 h**	**94**	**75**
				THF, –25 °C, 24 h	quant	71
3	 5c	 6c	1.74	DME, –25 °C, 24 h	0	–
				THF, –25 °C, 48 h	**65 (88)[e]**	**89**
4	 5d	 6d	1.74	DME, –25 °C, 24 h	quant	85
				THF, –25 °C, 24 h	**96**	**88**
5	 5e	 6e	1.77	**DME, –25 °C, 24 h**	**quant**	**68**
				THF, –25 °C, 24 h	quant	59
6	 5f	 6f	2.21	DME, –25 °C, 48 h	35	66
				THF, –25 °C, 24 h	**87**	**72[f]**
7	 5g	 6g	2.2	DME, –25 °C, 48 h	83	72
				THF, –25 °C, 24 h	**quant**	**76**
8	 5h	 6h	2.8	**toluene, –25 °C, 24 h**	**99**	**79**
9	 5i	 6i	>2.8[g]	**toluene, –25 °C, 24 h**	**quant**	**95**
10	 5j	 6j	>2.8[g]	**toluene, –25 °C, 24 h**	**quant**	**87**
11	 5k	 6k	>2.8[g]	**toluene, –25 °C, 24 h**	**91**	**78**

[a] Major enantiomer drawn; see text concerning determination of absolute configuration. [b] A-value of the substituent at the oxindole 3-position; source: Eliel, E. L.; Wilen, S. H. and Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994. [c] Isolated yield. [d] Determined by chiral HPLC. [e] Yield based on recovered starting material. [f] Approximate value as baseline separation of enantiomers could not be achieved. [g] A-value assumed to be larger than that for unsubstituted phenyl ring.

example **5h** (Table 1, entry 11), the same catalyst and temperature were optimal, except that toluene as the solvent proved to be superior (79% ee of **6h**).

The substrate scope of the reaction was explored next (Table 2). In terms of *N*-protection, both *N*-Me (**6a**) and *N*-Bn (**6b**) groups were compatible (Table 2, entries 1 and 2). Crucially, methyl- and phenyl-substitution on the allyl group was also tolerated well, affording products **6c** and **6d** in good to excellent yields and selectivity (Table 2, entries 3 and 4). An acetonitrile substituent (**6e**) led to a slight decrease in enantioselectivity (Table 2, entry 5), whereas the larger isopropyl and cyclohexyl substituents were found to provide products **6f** and **6g** but with the *opposite* absolute stereochemical configuration (Table 2, entries 6 and 7). Finally, a range of aryl substituents were tested in toluene as the solvent (Table 2, entries 8–11). The unsubstituted phenyl example as well as those with *ortho*- and *meta*-substituents were all successful, and the desired

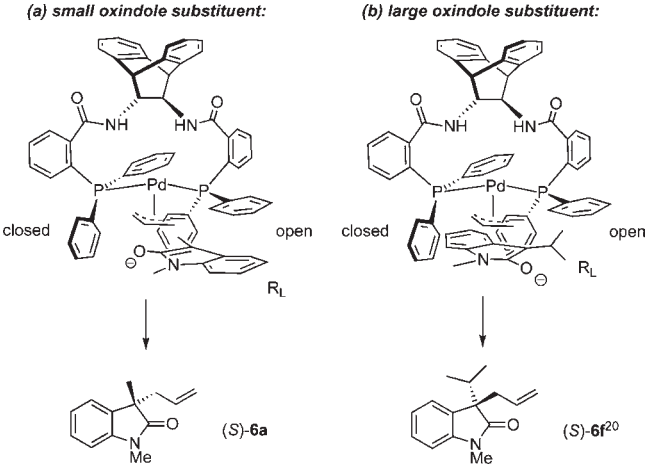
products **6h**–**k** were obtained in excellent yields and good to excellent enantioselectivity (quantitative yield and 95% ee of **6i**). The stereochemical configuration of **6h**–**k** was found to be the same as that for the isopropyl and cyclohexyl substituted oxindoles **6f** and **6g**. The absolute configuration of seven products was determined by comparison of optical rotation data with literature values (see Supporting Information for full details).[7a,16]

Speculating that the stereoselectivity of the reaction correlates with the steric size of the oxindole substituent, we utilized the A-values (on a cyclohexane ring) of these substituents as an approximate descriptor of steric/electronic bulk (Table 2).[17] Specifically, the absolute configuration of the major enantiomer of product appears to depend on whether the oxindole substituent is small (Table 2, entries 1–5, A-values 1.74–1.77) or large (Table 2, entries 6–11, A-values 2.2–2.8).

Taking the reasonable assumption[6b] that an outersphere mechanism is in operation (the oxindole enolate is a semistabilized anion, p$K_a \approx 18.5$), in the case of a small substituent (e.g., Me, Scheme 2a), the more sterically demanding oxindole moiety is placed under the "open flap",[18,19] leading to the observed stereochemical outcome. In contrast, the steric bulk of a larger substituent (e.g., *i*-Pr) overrides the steric effect exerted by the oxindole moiety and provides a product with the opposite stereochemical configuration (Scheme 2b).[20] Of course, the opposite enantiomers of the products could in principle be obtained by simply employing the opposite enantiomer of the chiral ligand.

In summary, we have developed a procedure for the asymmetric palladium-catalyzed allylation of both alkyl- and aryl-substituted oxindoles, installing an all-carbon quaternary stereogenic center in excellent yields and good to excellent enantioselectivity. We also report an unexpected reversal in stereoselectivity and postulate that this is governed by the steric size of the oxindole substituent. Access to enantioenriched oxindoles opens up new avenues for stereoselective natural product synthesis, which is the current focus of our work.

Scheme 2. Stereochemical Rationale



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Supporting Information Available. Full experimental procedures, characterization data, copies of HPLC traces and ^{1}H NMR spectra, as well as a summary of optical rotation data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A-values also reflect stereoelectronic factors involved in the equatorial/axial substitution preference on a cyclohexane ring and are, therefore, only a partial measure of steric bulk.

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(20) Both methyl-substituted **6a** and *iso*-propyl-substituted **6f** have the (*S*)-configuration, according to Cahn–Ingold–Prelog priority rules.