Asymmetric Catalysis

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An Asymmetric Aerobic Aza-Wacker-Type Cyclization: Synthesis of Isoindolinones Bearing Tetrasubstituted Carbon Stereocenters**

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Chiral amines bearing an α-tetrasubstituted carbon stereocenter are important structural motifs of potent drugs and bioactive natural products, and therefore, considerable effort has been directed toward their asymmetric synthesis.[1] A variety of useful asymmetric catalytic reactions involving the addition of nucleophiles to ketimines has been reported.[1,2] However, the transition-metal-catalyzed amination of alkenes to give chiral amines bearing an α-tetrasubstituted carbon stereocenter, remains unexploited and challenging.[3] Intramolecular amination of alkenes has attracted much attention because of the importance of nitrogen-containing heterocycles.[4–12] Oxidative aza cyclizations and their enantioselective variants are some of the most efficient intramolecular amination reactions.[6,7] The research group of Chemler has developed a family of elegant copper-catalyzed asymmetric intramolecular oxidative-amination reactions of alkenes, reactions that include haloamination,[8a] carboamination,[8b,c] aminooxygenation,[8d,e] and diamination.[8f] In addition, the research group of Yang has shown that it is possible to form two stereocenters in a highly enantioselective palladium-catalyzed aerobic tandem aza cyclization/Heck-type reaction.[9] Enantioselective palladium-catalyzed oxidative-aminocarbonylation reactions have also been reported.[10] However, the use of these catalytic asymmetric reactions is limited to the preparation of chiral cyclic amines bearing an α-trisubstituted carbon stereocenter.

Palladium-catalyzed aza-Wacker-type cyclizations are of longstanding interest.[11,12] Despite recent advances in this area,[12] efforts toward the development of enantioselective variants have had limited success, and highly enantioselective aza-Wacker-type cyclizations have only recently become feasible.[13] In contrast, asymmetric Wacker-type cyclizations have been relatively well-studied.[14] Whereas previously developed enantioselective aza-Wacker-type cyclizations gave amines bearing an α-trisubstitued carbon stereocenter, enantioselective aza-Wacker-type reactions that give chiral amines bearing an α-tetrasubstituted carbon stereocenter have not yet been established, despite some success in preparing such compounds in other metal-catalyzed intramolecular oxidative-amination reactions.[8–10] Herein, we describe an asymmetric palladium-catalyzed aza-Wacker-type cyclization that gives isoindolinones that contain a tetrasubstituted carbon stereocenter α to the nitrogen atom.

Recently, we developed a regioselective intramolecular aerobic aza-Wacker-type cyclization for the preparation of isoindolinones and isoquinolin-1(2*H*)-ones; trisubstituted olefin substrates were highly reactive under the reaction conditions ($Pd(OAc)_2$/1,10-phenanthroline/MeOH/O_2/60 °C) and gave isoindolinone products bearing tetrasubstituted carbon atoms α to the nitrogen atom.[15] We believed that an enantioselective variant of this reaction could be developed. These chiral isoindolinones can be found as structural motifs in biologically active natural products and drug candidates such as **1**,[16a] which is a renin inhibitor, **2**,[16b] which is a drug for the treatment of cardiac arrhythmias, and **3**, which is a modulator of serotonin receptors (Figure 1).[16c]

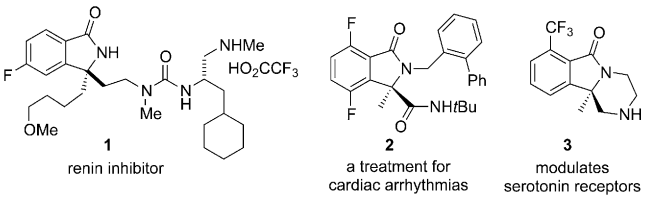
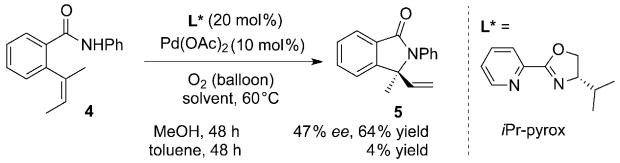


Figure 1. Representative examples of isoindolinones bearing tetrasubstituted carbon stereocenters α to the nitrogen atom.

In initial attempts to effect the transformation, we tested reaction conditions used previously by both our research group (MeOH/O_2)[15] and the research groups of others (toluene/O_2; Scheme 1).[9,13] When using the chiral pyridine–oxazoline ligand, *i*Pr-Pyrox, together with $Pd(OAc)_2$ as the metal source, the transformation of substrate **4** was much more efficient in MeOH than it was in toluene and the product was isolated with a moderate *ee* value. We decided to use a more reactive substrate, and chose compound **6**, which is



Scheme 1. Initial experiments to explore the catalytic reaction.

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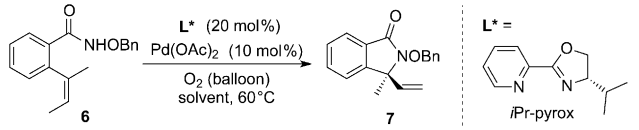
Table 1: A solvent screen.[a]

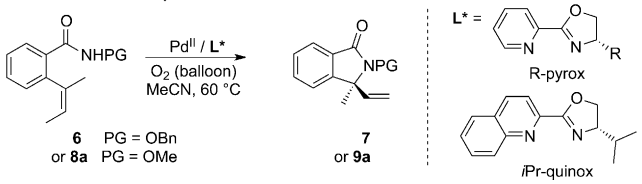


6 7

Entry	Solvent	t [h]	Yield [%][b]	*ee* [%][c]
1	toluene	24	71	21
2	DCE	24	68	54
3	1,4-dioxane	24	65	24
4	MeOH	12	99	66
5	EtOH	12	98	52
6	*i*PrOH	24	73	47
7	*t*AmylOH	24	46	35
8	CF_3CH_2OH	24	81	29
9	DMF	12	95	70
10	DMA	24	78	67
11	NMP	24	75	66
12	acetone	24	94	57
13	DMSO	12	90	68
14	MeCN	12	99	79

[a] Reactions were carried out on a 0.20 mmol scale using $Pd(OAc)_2$ (10 mol%) and ligand (20 mol%) in solvent (2.0 mL) under O_2 (1 atm) at 60 °C. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. Bn = benzyl, DCE = dichloroethane, DMA = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, NMP = *N*-methylpyrrolidinone.

Table 2: Further optimization of reaction conditions.[a]



6 PG = OBn or **8a** PG = OMe **7** or **9a**

Entry	Substrate	Pd^{II}	L*	*t* [h]	*ee* [%][b]
1	**6**	$Pd(OAc)_2$	*i*Pr-pyrox	12	79
2[c]	**6**	$Pd(OAc)_2$	*i*Pr-quinox	24	9
3	**6**	$Pd(OAc)_2$	Ph-pyrox	12	59
4	**6**	$Pd(OAc)_2$	Bn-pyrox	12	81
5	**6**	$Pd(OAc)_2$	*t*Bu-pyrox	12	81
6	**6**	$Pd(tfa)_2$	*t*Bu-pyrox	10	89
7[d]	**6**	$Pd(tfa)_2$	*t*Bu-pyrox	4	94
8[d,e]	**6**	$Pd(tfa)_2$	*t*Bu-pyrox	48	95
9[d]	**8a**	$Pd(tfa)_2$	*t*Bu-pyrox	3	97
10[d]	**8a**	$Pd(tfa)_2$	Bn-pyrox	3	85
11[d,f]	**8a**	$Pd(tfa)_2$	*t*Bu-pyrox	9	96
12[d,g]	**8a**	$Pd(tfa)_2$	*t*Bu-pyrox	96	86

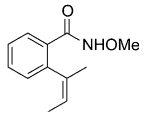
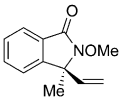
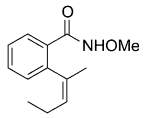
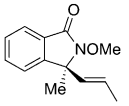
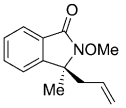
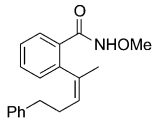
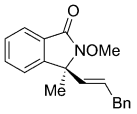
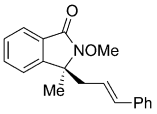
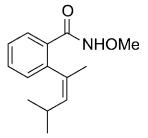
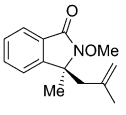
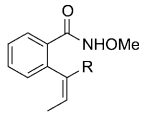
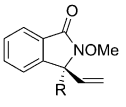
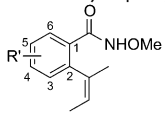
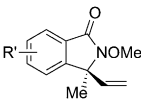
[a] Unless otherwise stated, reactions were carried out on a 0.20 mmol scale using 10 mol% Pd^{II} and 20 mol% ligand in MeCN (2.0 mL) under 1 atm dioxygen at 60 °C. Yields of isolated product were 99%. [b] Determined by HPLC using a chiral stationary phase. [c] Yield was 61%. [d] 4 Å molecular sieves (80 mg) was added. [e] Reaction temperature was 30 °C and the yield was 81%. [f] Pd^{II} (5.0 mol%) and ligand (7.5 mol%) were used. [g] Pd^{II} (1.0 mol%) and ligand (1.2 mol%) were used and the yield was 76%. tfa = trifluoroacetate.

different from compound **4** in that it contains the more electron-withdrawing and easily removable *N*-OBn group (Table 1).[14e,g] Again, the reaction was more efficient in MeOH than it was in toluene (Table 1, entries 1 and 4).[17] We then screened different solvents to improve the enantioselectivity (Table 1). The use of strongly coordinating solvents gave the best yields and the highest levels of enantioselectivity; for example, when the reaction was performed in solvents such as MeOH, DMF, and DMSO, the results were better than when it was performed in toluene, DCE, and 1,4-dioxane (Table 1, compare entries 4, 9, and 13 with entries 1–3). The use of alcohol solvents with smaller alkyl group gave products with higher *ee* values (Table 1, entries 4–7). The enantioselectivity of the reaction appears to be adversely affected by solvents of relatively high acidity: when the solvent is changed from ethanol to the isosteric yet more acidic solvent, CF_3CH_2OH, the *ee* value of the product drops from 52 to 29% (Table 1, entries 5 and 8). Among the acyl-containing solvents, the use of DMF provided the best result (Table 1, entries 9–12). The highest level of enantioselectivity was achieved when using MeCN as the solvent, a result that may due to its small size and its ability to coordinate strongly through its nitrogen atom (Table 1, entry 14).

With the optimum solvent established, we then screened other variables such as metal source, ligand, and time of reaction (Table 2). When using $Pd(OAc)_2$ as the palladium source, without an additive, the use of *t*Bu-Pyrox and Bn-Pyrox as ligands provided the highest *ee* values (Table 2, entries 1–5). The use of the sterically hindered quinolone–oxazoline ligand, *i*Pr-Quinox, gave a low yield and a low level of enantioselectivity (Table 2, entry 2).[13] The efficiency and enantioselectivity of the reaction could be further enhanced by changing the metal source from $Pd(OAc)_2$ to $Pd(tfa)_2$ and by adding molecular sieves (Table 2, entries 6 and 7). Unlike the previously reported asymmetric aza-Wacker-type cyclization,[13] reducing the reaction temperature did not lead to a significant increase in the *ee* value (Table 2, entry 8). This result may be due to the difficulty of MeCN in dissociating from the metal center of the catalyst or a catalytic intermediate at low temperature.[18] The use of substrate **8a**, which has a relatively small N protecting group (*N*-OMe), gave a higher *ee* value (Table 2, entry 9). The use of the ligand, Bn-Pyrox, gave a lower level of enantioselectivity than that of *t*Bu-Pyrox under the same reaction conditions (Table 2, entry 10). Decreasing the catalyst loading from 10 to 5 mol% did not obviously affect the results (Table 2, entry 11). The catalyst amount could be further decreased to 1 mol% without a significant decrease in enantioselectivity if the reaction time was increased (Table 2, entry 12). Based on the above results, the optimized reaction conditions are as follows: *t*Bu-Pyrox (7.5 mol%) as the chiral ligand, $Pd(tfa)_2$ (5.0 mol%) as the palladium source, MeCN as the solvent, 4 Å molecular sieves as an additive, and 60 °C as the reaction temperature.

Having optimized reaction conditions established, a variety of substrates were examined (Table 3). The use of substrates containing different terminal substituents on the olefin moiety gave quantitative yields and good levels of enantioselectivity (Table 3, entries 1–4). When the terminal substituent of the olefin moiety in the substrate was an ethyl or a 2-phenylethyl group, a mixture of olefin isomers were

Table 3: Substrate scope.[a,b,c]

Entry	8	t [h]	9 ee [%] (Yield [%])	
1	 **8a**	9		 **9a**: 96 (99)
2	 **8b**	9	 **9b**: 96 (33)	 **9b'**: 99 (66)
3	 **8c**	9	 **9c**: 96 (74)	 **9c'**: 98 (25)
4	 **8d**	9		 **9d**: 94 (95)
				
5	**8e**: R = Et	9		**9e**: 94 (99)
6	**8f**: R = *n*Pr	9		**9f**: 94 (99)
7	**8g**: R = CH_2CH_2Ph	9		**9g**: 92 (99)
8	**8h**: R = cyclopentyl	9		**9h**: 91 (99)
				
9	**8i**: R′ = 4-MeO	18		**9i**: 91 (90)
10	**8j**: R′ = 4-Cl	18		**9j**: 96 (99)
11	**8k**: R′ = 4-F	12		**9k**: 97 (99)
12	**8l**: R′ = 5-MeO	18		**9l**: 91 (92)
13	**8m**: R′ = 6-MeO	36		**9m**: 88 (71)
14	(*E*)-**8n**: R′ = 3-Me	18		**9n**: 57 (97)

[a] Reactions were carried out on a 0.20 mmol scale using $Pd(tfa)_2$ (5.0 mol%), ligand (7.5 mol%), and 4 Å molecular sieves (80 mg) in MeCN (2.0 mL) under O_2 (1 atm; balloon) at 60°C. [b] Yields of isolated product. [c] The *ee* values were determined by HPLC using a chiral stationary phase.

obtained (Table 3, entries 2 and 3). The substrate with isopropyl as the terminal substituent only gave the terminal alkene product in high yield with an *ee* value of 94% (Table 3, entry 4). Interestingly, the *ee* values of olefin products **9b′** and **9c′** were higher (up to 99%) than those of the normal aza-Wacker-type products **9b** and **9c**. This difference in *ee* value may be due to kinetic resolution in the isomerization step that gives products **9b′** and **9c′**, a resolution that is possible because both the compound undergoing isomerization and the isomerization catalyst are chiral. As the size of the internal substituent (R group) of the olefin moiety in the substrate increases, the enantioselectivity of the reaction decreases slightly (Table 3, entries 1, and 5–8); however, all products were still obtained in nearly quantitative yield. The presence of an electron-donating group on the benzene ring led to a decrease in both the yield and the enantioselectivity (Table 3, entries 9, 12, and 13); on the other hand, the presence of an electron-withdrawing group showed no effect on the results (Table 3, entries 10 and 11). Substitution at the position *ortho* to the acyl group is also tolerated, but the reactivity of the corresponding substrate **8m** is relatively low (36 h, 71% yield; Table 3, entry 13). Although the reaction of substrate **8n**, which contains a substituent at the position *ortho* to the olefin group, was efficient, the *ee* value of the product was relatively low (57%) owing to the *E* geometry of the olefin moiety (Table 3, entry 14).[17,19]

The absolute configuration of the product **9j** was determined to be *S* by X-ray crystallographic analysis (Figure 2).[20] This stereochemical outcome can be explained using the model of Stahl and co-workers (Scheme 2).[13c] The nitrogen

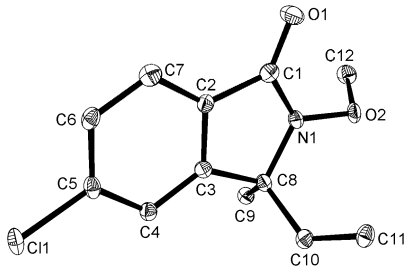
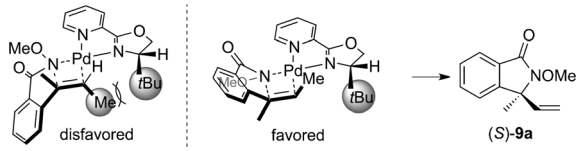


Figure 2. ORTEP representation of **9j**; thermal ellipsoids are shown at 30% probability and hydrogen atoms are omitted for clarity.

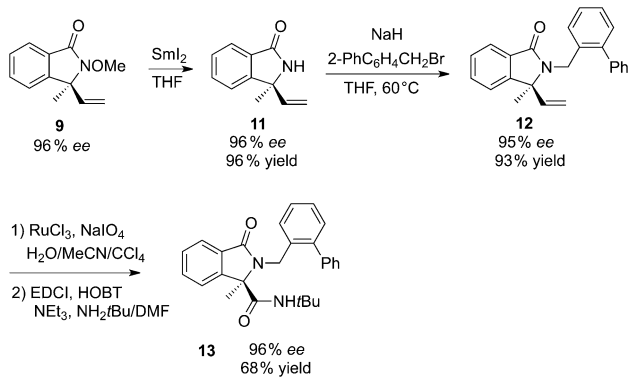


Scheme 2. Model for explaining the origin of asymmetric induction.

atom of the methoxyamine moiety in the substrate is bound to the Pd center and is *cis* to the pyridine moiety of Pyrox; the olefin moiety is bound at the position that is *trans* to the pyridine moiety. When the olefin moiety of the substrate has *Z* geometry, the terminal methyl group of the olefin is oriented upward, and thus away from the *tert*-butyl group, in the favored transition state. *syn*-Aminopalladation thus leads to (*S*)-**9**.[21] The strongly coordinating solvent may function as a ligand to promote both the formation and the further transformation of the above-mentioned Pd complex.[18]

The OMe group could be removed by SmI_2-promoted reductive cleavage of the O–N bond in 96% yield without a reduction in *ee* value (Scheme 3). Then, introduction of a biphenyl-2-ylmethyl group on the nitrogen atom followed by oxidation of the olefin group and a condensation reaction with *tert*-butyl amine gave **13**, an analogue of drug **2**, in high overall yield with 96% *ee*.

In summary, we have developed an efficient catalytic enantioselective aza-Wacker-type cyclization reaction that



Scheme 3. Further transformation of an isoindolinone product. EDCI = 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide, HOBt = 1-hydroxybenzotriazole.

gives isoindolinones that contain a tetrasubstituted carbon stereocenter α to the nitrogen atom. A wide range of substrates gave excellent yields and high levels of enantioselectivity (up to 99% yield and 99% *ee*).

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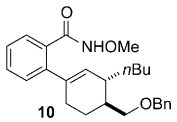
[17] The reaction of (*E*)-**6** showed high efficiency but low enantioselectivity (99% yield, 33% *ee*). The *N*-OBn 1,2-disubstituted olefin substrate showed no reactivity under the optimized reaction conditions. See also Ref. [15].

[18] For a more detailed explanation, see the Supporting Information.

[19] We could not obtain (*Z*)-**8n**, presumably because of steric hindrance.

[20] CCDC 882841 (**9j**) contain 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.

[21] We have studied the aminopalladation step using *Z*-configured substrate **10**. The results suggest that the mechanism involves *syn* aminopalladation. For a study of the mechanism of carbopalladation using a similar strategy, see: a) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578 – 9579; b) H. Zhang, E. M. Ferreira, B. M. Stoltz, *Angew. Chem.* **2004**, *116*, 6270 – 6274; *Angew. Chem. Int. Ed.* **2004**, *43*, 6144 – 6148.



Communications

Asymmetric Catalysis

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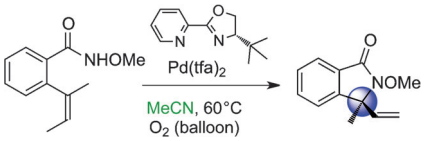
An Asymmetric Aerobic Aza-Wacker-Type Cyclization: Synthesis of Isoindolinones Bearing Tetrasubstituted Carbon Stereocenters



It's all in the solvent: An enantioselective variant of an aza-Wacker-type cyclization that gives isoindolinones containing tetrasubstituted carbon centers α to the nitrogen atom has been developed (see scheme; tfa = trifluoroacetate). The use of a highly coordinating solvent is crucial for the activity of the catalyst and the stereoselectivity the reaction (up to 99% *ee*).

