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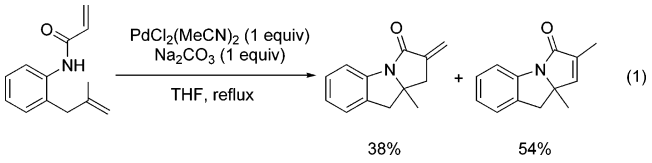
Pd(II)-Catalyzed Enantioselective Oxidative Tandem Cyclization Reactions. Synthesis of Indolines through C−N and C−C Bond Formation

Kai-Tai Yip, Min Yang, Ka-Lun Law, Nian-Yong Zhu, and Dan Yang*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

Received January 15, 2006; E-mail: yangdan@hku.hk

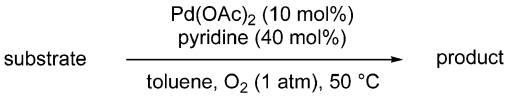
Palladium-catalyzed tandem cyclization reactions are versatile and powerful tools to construct complex polycyclic products because multiple stereocenters can be established in one step under mild conditions.[1] In contrast to the well-developed asymmetric tandem cyclization reactions catalyzed by chiral palladium(0) complexes, asymmetric oxidative tandem cyclization reactions involving palladium(II) complexes have received relatively little attention, despite the fact that the latter reactions have an advantage in that C−X bonds are formed to generate heterocyclic molecules,[2] many of which are core structures of potent drugs and bioactive natural products.[3] The presence of cocatalysts (e.g., copper salts) or organic oxidants (e.g., benzoquinone), which are used to regenerate Pd(II) species, in oxidative Pd(II) catalysis complicates the development of asymmetric transformation. Previously, the only successful Pd(II)-catalyzed enantioselective oxidative tandem cyclization reactions were reported by Sasai,[4] whose Wacker-type tandem cyclization of alkenyl alcohols afforded bicyclic product with excellent enantiomeric excess (up to 95%). Herein we describe the first enantioselective oxidative tandem cyclizations under Pd(II) catalysis using nitrogen atom-based nucleophiles and molecular oxygen as the sole oxidant.

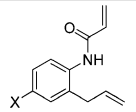
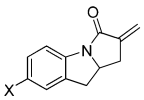
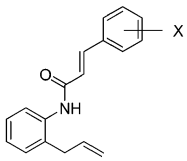
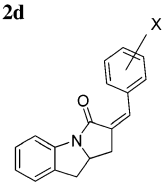
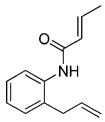
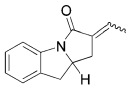
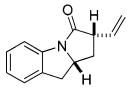
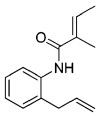
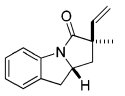
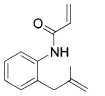
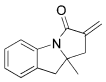


(1)

Although an aza-Wacker-type tandem cyclization using a stoichiometric amount of Pd(II) complex was reported previously by Hegedus and co-workers (eq 1),[5] that reaction required tandem relay (using a 1,1-disubstituted alkene)[6] and led to double-bond-isomerized products. Initially, we chose the Pd(II)/pyridine catalyst system for our studies of tandem cyclization reactions because it is effective for a number of mechanistically distinct oxidative reactions, including oxidation of alcohols, Wacker oxidation, oxidative C−C bond cleavage, and oxidative cyclization.[7] Indeed, successful Pd(II)-catalyzed oxidative tandem cyclization of **1** occurred to afford **2** and/or **3** exclusively without the formation of any undesired monocyclization products (Table 1).[8] We evaluated substrates **1a**−**d**, which bear different *para*-substituents, and observed a general trend (entries 1−5) relating to the electronic effects that the *para*-substituents have on reactivity (Cl ≈ H > Me > OMe); for example, substrate **1b**, which possesses an electron-withdrawing group (X = Cl), cyclized more efficiently than substrates **1c** and **1d** did, which bear electron-donating groups (X = Me and OMe, respectively). The product yield remained excellent even when the catalyst loading was decreased to 5 mol % (entry 2). When pyridine was employed as the ligand, incomplete conversions of substrates **1c** and **1d** occurred, even after prolonged heating. In contrast, the cyclizations of **1c** and **1d** proceeded smoothly when using triphenylphosphine as the ligand (entries 4 and 5). Interestingly, substrates **1e**−**g**, which exist in the *E* configuration, afforded exclusively the products **2e**−**g** in *Z* configurations in good yields (entries 6−8). When the crotyl derivative **1h** was employed, two different products **2h** and **3h** were isolated (entry 9). Unlike **2e**−**g**, **2h** existed as a mixture of *E* and *Z* isomers. The major product **3h** possesses two stereogenic centers that were established in a single step from **1h**. Interestingly, **3i**, which possesses an α-methyl substituent, was obtained from **1i** in excellent diastereoselectivity (entry 10). Similar

Table 1. Pd(II)-Catalyzed Oxidative Tandem Cyclization Reactions[a]



entry	substrate	product	time (h)	yield (%)[b]
1				
	1a X = H	**2a**	19	95
2[c]	**1a** X = H	**2a**	25	91
3	**1b** X = Cl	**2b**	19	83
4[d]	**1c** X = Me	**2c**	22	85
5[d]	**1d** X = OMe	**2d**	48	74
6				
	1e X = H	**2e**	23	84
7	**1f** X = 3-Cl	**2f**	36	88
8	**1g** X = 4-Me	**2g**	19	83
9			20	10 (**2h**)[e]
	1h	**2h**		
				70 (**3h**) (dr 1.8:1)[f]
		3h		
10			36	50 (dr 24:1)[f]
	1i	**3i**		
11[g]			48	91
	1j	**2j**		

[a] Unless otherwise indicated, all reactions were performed at 50 °C using the substrate (0.3 mmol), pyridine (40 mol %), and $Pd(OAc)_2$ (10 mol %) in toluene (3 mL) under O_2 (1 atm). [b] Yield of isolated product. [c] Pyridine (20 mol %), $Pd(OAc)_2$ (5 mol %). [d] PPh_3 (40 mol %) was used instead of pyridine. [e] Ratio of stereoisomers was not determined. [f] Ratio determined from ^1H NMR spectra; the major diastereomer is depicted. [g] Quinoline (40 mol %) was used instead of pyridine.

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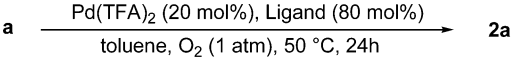
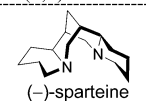
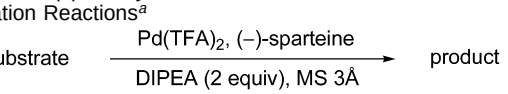
Table 2. Optimization of Reaction Conditions[a]

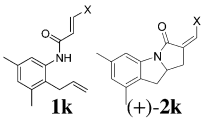


entry	ligand[b]	conv (%)[c]	yield (%)[c]	ee (%)[d]
1	$(DHQ)_2PHAL$	100	89	12
2	$(DHQ)_2AQN$	100	94	12
3	$(DHQD)_2PYR$	100	98	8
4	(−)-cinchonidine	86	40	7
5	hydroquinine	52	47	11
6	(*S*,*S*)-Ph-box	94	55	9
7		49	29	54
8[e]		70	41	73
9[e,f]		97	68	74
10[e,f,g]	(−)-sparteine	93	75	86

[a] Unless otherwise indicated, all reactions were performed at 50 °C using the substrate **1a** (0.2 mmol), $Pd(TFA)_2$ (20 mol %), and the ligand (80 mol %) in toluene (2 mL) under O_2 (1 atm). [b] For the structures of the different chiral ligands, see the Supporting Information. [c] Determined from ^1H NMR spectra using nitrobenzene as the internal standard. [d] Determined through HPLC analysis using a Chiralcel OD column. [e] Molecular sieves (3 Å) (500 mg/mmol substrate) were added. [f] Reaction temperature was 80 °C. [g] DIPEA (2 equiv) was added.

Table 3. Pd(II)-Catalyzed Enantioselective Oxidative Tandem Cyclization Reactions[a]



entry	substrate	product	$Pd(TFA)_2$ (mol%)[b]	time (h)	yield (%)[c]	ee (%)[d]
1			20	24	75	83
2	**1a**	(+)-**2a**	10	26	78	86
3			5	35	70	86
4	**1b**	(+)-**2b**	20	48	61	75
5	**1f**	(+)-**2f**[e]	20	48	60	80
6	**1h**	(+)-**2h**	20	48	15 (**2h**)	82
		(+)-**3h**			63 (**3h**)	80
					(dr 8:1)	(86)[f]
7						
	1k X = H	(+)-**2k**	10	26	63	91
8	**1l** X = *m*-ClPh	(+)-**2l**	10	26	64	87

[a] Unless otherwise indicated, all reactions were performed at 80 °C using the substrate (1 mmol), activated 3 Å molecular sieves (500 mg/mmol substrate), DIPEA (2 equiv), $Pd(TFA)_2$, and (−)-sparteine in toluene (10 mL) under O_2 (1 atm). [b] Ratio of $Pd(TFA)_2$ to (−)-sparteine was maintained at 1:4. [c] Yield of isolated product. [d] Enantiomeric excess was determined through HPLC analysis using a Chiralcel OD column. [e] Absolute configuration of the product **2f** was determined to be *S* through X-ray analysis. [f] Value of enantiomeric excess of the minor diastereomer of **3h**.

to **2a**−**h**, the exocyclic alkene moiety in **2j** is stable under the optimized reaction conditions, and no isomerized product was isolated (entry 11); thus, these conditions are superior to those reported by Hegedus (eq 1).[5]

To explore an asymmetric version of this tandem cyclization reaction, we screened a variety of reaction parameters for the reaction of **1a**, including the use of chiral ligands, various temperatures, and the presence of additives were screened (Table 2). Although the use of quinine- and quinidine-derived ligands led to high yields (>89%), **2a** with poor values of enantiomeric excess was obtained (<12%; entries 1−3). Other structurally distinct ligands (entries 4−6) failed to provide satisfactory yields and enantioselectivities, with the exception of (−)-sparteine,[9] which emerged as the most promising ligand: it provided values of enantiomeric excess of up to 54% (entry 7). Further optimization of the reaction conditions—that is, adding activated 3 Å molecular sieves (entry 8), increasing the reaction temperature to 80 °C (entry 9), and employing the bulky tertiary amine diisopropylethylamine (DIPEA; entry 10)—led to pronounced improvements in both the catalytic activity (yields of up to 75%) and enantioselectivity (up to 86% ee).

Under the optimized conditions and using the chiral Pd(II)/(−)-sparteine complex, a variety of chiral tandem cyclization products **2** and **3** were obtained with good to excellent enantioselectivities (Table 3). A comparably high enantiomeric excess of **2a** was achieved even when the loading of the chiral Pd(II)/(−)-sparteine catalyst was decreased to 5 mol % (entries 1−3). The cyclization of **1b**, which possesses a *para*-chloro substituent, proceeded slower than that of **1a** (entry 4 vs 1). Cyclization of substrate **1f**, which possesses a cinnamyl group, afforded **2f** in the *S* configuration, but without a significant improvement in the value of the enantiomeric excess (80% ee, entry 5 vs 1); in contrast, the presence of *meta*-methyl substituents on the aniline moiety (**1k** and **1l**) enhanced the product enantioselectivity (**2k**, 91% ee, entry 7 vs 2; **2l**, 87% ee, entry 8 vs 5). Relative to the $Pd(OAc)_2$/pyridine system, it is noteworthy that the $Pd(TFA)_2$/(−)-sparteine complex improved the diastereomeric ratio of product **3h** from 1.8:1 to 8:1 (entry 9 of Table 1 vs entry 6 of Table 3).

In summary, we have developed a Pd(II)-catalyzed enantioselective oxidative tandem cyclization using readily available (−)-sparteine as the chiral ligand and molecular oxygen as a green oxidant. This methodology provides direct access to enantioenriched and structurally versatile indolines. We are currently undertaking mechanistic studies of this oxidative tandem cyclization, and the results will be reported in due course.

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Supporting Information Available: Preparation and characterization of **1**−**3**; HPLC analysis of chiral products **2**−**3** and X-ray structures of **2a** and (+)-**2f** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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