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Kinetic Resolution of Indolines by Pd-Catalyzed Asymmetric Allylic Amination

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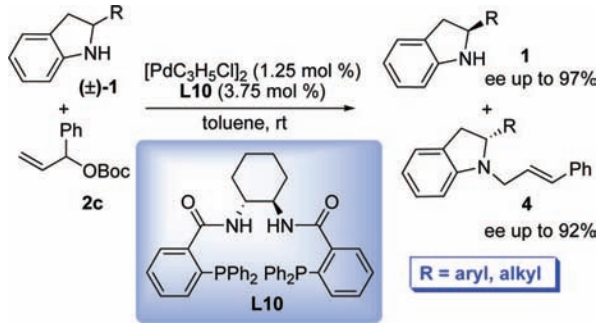
ABSTRACT



The kinetic resolution of indolines was realized via a Pd-catalyzed allylic substitution reaction by using Trost's chiral ligand L10, affording optically active indolines and N-allylated indolines in high yields and high enantioselectivities with an *S* factor up to 59, which provided the first example for the kinetic resolution of nucleophiles via a transition-metal-catalyzed allylic substitution reaction.

The palladium-catalyzed asymmetric allylic substitution reaction is one of the most powerful tools for constructing chiral centers via carbon−carbon and carbon−heteroatom bond-forming reactions.[1] A diversity of bonds can be formed, and chiral elements can be installed in either the nucleophile or the electrophile, or in both.[2−4] The scope of the nucleophiles has not been limited to those "soft" examples. Despite such great progress, the installment of a chiral center on the nucleophiles has been limited to reactions using carbon nucleophiles, establishing the chiral center at α-position of carbonyl group. On the other hand, kinetic resolution is a powerful protocol in asymmetric catalysis to afford optically active molecules by using racemic starting material.[5] The strategy has also been successfully applied in the Pd-catalyzed allylic substitution reaction to resolve racemic allyl substrates,[6] However, no report has appeared on the kinetic resolution of nucleophiles via transition-metal-catalyzed

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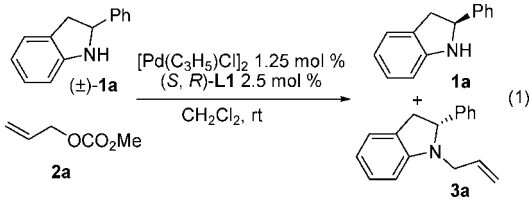
allylic substitution reaction. Recently, we developed several protocols to generate a chiral center on nucleophiles by the Pd-catalyzed asymmetric allylic alkylation reaction.[4] We wondered whether we could take advantage of kinetic resolution to resolve nucleophiles via Pd-catalyzed allylic substitution reaction. In this paper, we address this question and disclose our preliminary results on the kinetic resolution of indolines via Pd-catalyzed allylic amination reaction.

Chiral indolines are found in a variety of natural and biologically active products.[7] Only a few examples of catalytic asymmetric synthesis are described,[8,9] and an effective process still remains to be explored. Thus, indoline **1** was selected as the nucleophile in our investigation. At first, 2-phenylindoline **1a** was subjected to the reaction with 0.5 equiv of allyl acetate **2a** in the presence of the ferrocene ligand (*S*,*R*)-**L1** at room temperature; allylated indoline **3a** was provided in 16% yield and in 6% ee while **1a** was recovered in 80% yield and in 3% ee (eq 1).



To improve the efficiency of the reaction, the impact of parameters, including bases, solvents, and allyl reagents as well as the structure of ligands, were investigated (eq 2, Table 1). By employing Et_3N or K_2CO_3, the ee value of both **1a** and **3a** increased (entries 2 and 3). The addition of NaOAc improved the results further, providing **3a** in 49% yield, 54% ee and **1a** in 46% yield, 51% ee (entry 4).[10] Screening of common solvents showed that DME was the best choice over CH_2Cl_2, (entry 4) ether, THF, dioxane, hexane, and toluene (not shown in Table 1). No significant changes were given when cinnamyl carbonate **2b** or branched allylic carbonate **2c** was used (entry 10 vs entries 11 and 12).

Table 1. Optimization of Reaction Parameters[a]

					3a or **4a**		**1a**	
entry	**L**	**2**	solvent	base	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)
1	**L1**	**2a**	CH_2Cl_2		16	6	80	3
2	**L1**	**2a**	CH_2Cl_2	Et_3N	49	8	46	10
3	**L1**	**2a**	CH_2Cl_2	K_2CO_3	49	26	46	51
4	**L1**	**2a**	CH_2Cl_2	NaOAc	49	54	46	56
5	**L1**	**2a**	DME	NaOAc	46	69	50	50
6	**L2**	**2a**	DME	NaOAc	43	26	50	ND
7	**L3**	**2a**	DME	NaOAc	49	23	42	ND
8	**L4**	**2a**	DME	NaOAc	49	73 (−)[d]	50	70 (−)[d]
9	**L5**	**2a**	DME	NaOAc	48	29 (−)[d]	47	ND
10	**L6**	**2a**	DME	NaOAc	40	74	52	54
11	**L6**	**2b**	DME	NaOAc	28	78	70	34
12	**L6**	**2c**	DME	NaOAc	37	73	59	53
13	**L7**	**2a**	DME	NaOAc	48	3.5	50	ND
14	**L8**	**2a**	DME	NaOAc	13	1	80	ND
15	**L9**	**2a**	DME	NaOAc	23	7	76	ND
16[e]	**L10**	**2a**	DME	NaOAc	39	53	47	47
17[e]	**L10**	**2c**	toluene	NaOAc	45	92	49	77
18[e]	**L10**	**2c**	toluene		42	89	50	83
19[e,f]	**L10**	**2c**	toluene		45	91	48	82

[a] Molar ratio of **1a**/**2**/$[Pd(C_3H_5)Cl]_2$/**L**/base = 100:50:1.25:2.5:100. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reversed sequence of peaks by HPLC. [e] 3.75 mol % of **L10** was used. [f] Reaction was carried out at 0 °C.

The structure of the ferrocene ligands is critical in this kinetic resolution. It is shown that the chiral elements in ligand **L4** are matched while those in ligands **L3**, **L5**, and **L6** are not; 49% yield of **3a** with 73% ee and 50% recovery of **1a** with 70% ee were afforded by using **L4** (entry 8 vs entries 7, 9, and 10). It was also found that the configuration of product was determined by that of the binol subunit (entries 8 and 9 vs entries 7 and 10).[4d] Ligand **L4** with *i*-Pr at oxazoline ring gave better results than **L1** and **L2** with H as substituent (entry 8 vs entries 5 and 6). The investigation of ligands, including PHOX,[11a,b] FcPHOX,[11c−e] BINAP,[11f] and Trost's chiral ligand **L10**,[11g−i] revealed that better results were obtained when **L10** was the ligand (entry 16 vs entries 13−15). Even better results were provided if the reaction proceeded in toluene and branched allylic carbonate **2c** was

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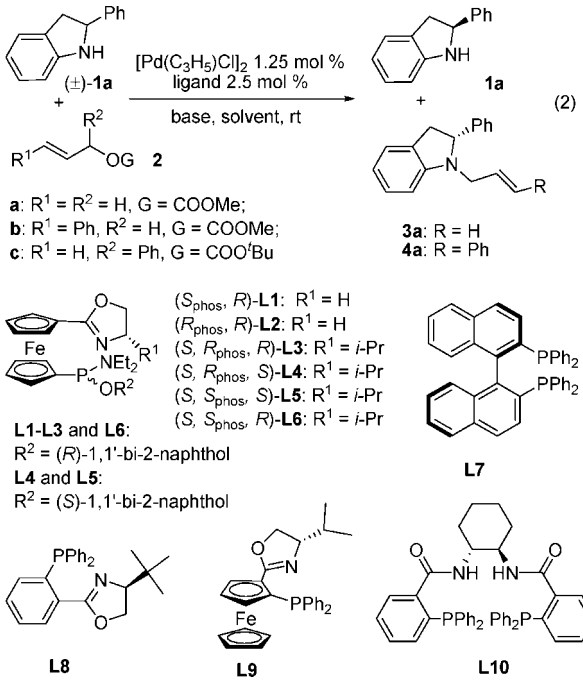
used, giving **4a** in 45% yield, 92% ee and **1a** in 49% yield, 77% ee (entry 17). No change in the enantioselectivity was observed when the reaction proceeded at 0 °C (entry 19) or in the absence of NaOAc (entry 18).



Having established the optimal conditions, the scope of indolines with different substituents was investigated (eq 3, Table 2). Using ligand **L10** in toluene at room temperature,

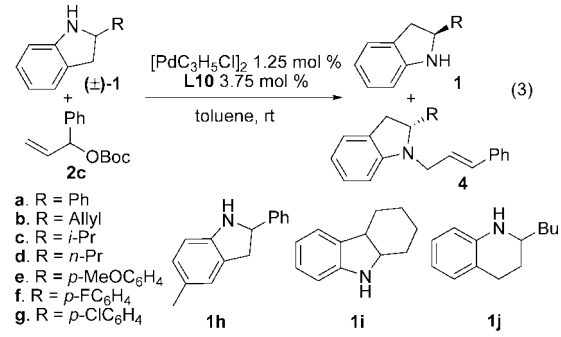
Table 2. Kinetic Resolution of Indolines **1**[a]

		4		1		
entry	indoline	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)	S[d]
1	**1a**	42	89	50	83	44
2	**1b**	48	65	47	43	7
3	**1c**	49	65	48	58	8
4	**1d**	40	61	48	36	6
5	**1e**	38	92	46	80	59
6	**1f**	34	90	40	82	48
7	**1g**	38	86	43	94	47
8	**1h**	42	83	34	97	44
9	**1i**	41	52	42	36	4
10	**1j**	37	57	44	42	5

[a] Molar ratio of **1**/**2c**/[Pd(C$_3$H$_5$)Cl]$_2$/**L 10** = 100:50:1.25:3.75. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Calculated by the method described by Kagan.[5a]

all substituted indolines were suitable substrates, providing optically active N-allylated indolines **4** in yields of 34−48% and ee's of 61−92%, accompanied by the recovered indolines in yields of 34−50% and ee's of 36−97%,with an S factor between 6 and 59.[12] High enantioselectivities with high S value were realized when 2-arylindolines were used (entries 1 and 5−8), despite the presence of an electron-donationg group (entry 5) or electron-withdrawing group (entries 6 and 7) at the 2-position of the indolines; good ee's were obtained if alkyl and allyl groups were at the 2-position of the indoline (entries 2−4), but the S value was lower. In addition to the indolines, other N-heterocycles, such as *cis*-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole **1i** (entry 9) and 2-butyl-1,2,3,4-tetrahydroquinoline **1j** (entry 10), were also suitable substrates for this kinetic resolution procedure, although the ee values were not good enough.

The absolute configuration of **1a** was determined to be S by comparing its optical rotation and HPLC trace with that reported by Gotor.[9]



In summary, we have realized the kinetic resolution of indolines via Pd-catalyzed allylic amination. Trost's chiral ligand **L10** showed its superiority among the ligands investigated. To the best of our knowledge, this is the first report to succeed in the kinetic resolution of nucleophiles via transition-metal-catalyzed allylic substitution, which provides a new access to the optically active nucleophiles. Further investigations on the reactions using other types of nucleophiles are in progress.

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Supporting Information Available: General procedure for Pd-catalyzed kinetic resolution of **1** and NMR and HPLC spectra of optically active indolines **1** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) S: selectivity factor = (rate of fast-reacting enantiomer/rate of slow-reacting enantiomer); see ref 5a.