Organic LETTERS

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Kinetic Resolution of 2-Substituted 2,3-Dihydro-4-pyridones by Palladium-Catalyzed Asymmetric Allylic Alkylation: Catalytic Asymmetric Total Synthesis of Indolizidine (−)-209I

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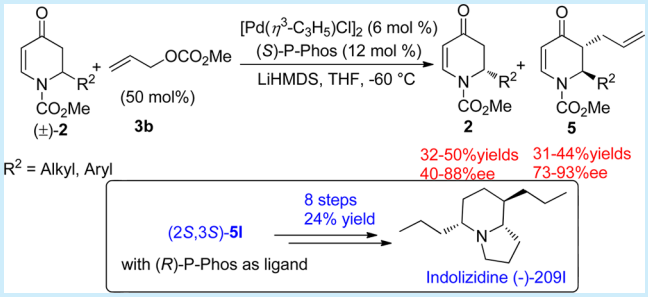
Supporting Information

ABSTRACT: The kinetic resolution of 2-substituted-2,3-dihydro-4-pyridones was realized via a Pd-catalyzed allylic substitution reaction using a commercially available (*S*)-P-Phos as a ligand, affording optically active dihydropyridones and C-allylated dihydropyridones in high yields and good enantioselectivities with the *S*-factor up to 43. With this protocol, a catalytic asymmetric total synthesis of indolizidine (−)-209I was realized for the first time.



Dihydropyridones are extraordinarily versatile intermediates and attractive building blocks for the synthesis of piperidine-containing molecules.[1] Indeed, this heterocycle exists in numerous drugs and drug candidates as an indispensable binding element.[2] Meanwhile, the piperidine moiety is prevalent in biologically active natural products such as indolizidines and quinolizidines. The chemistry of dihydropyridone is rich because it contains multiple nucleophilic sites and two electrophilic sites, which enables 2,3-dihydro-4-pyridones to be involved in a plethora of selective transformations such as *N*-functionalization, 1,2-addition of a carbonyl group, conjugated addition, and [2 + 2] cylization.[3] Many procedures have been developed to synthesize these heterocyclic compounds; however, efficient protocols to access the optical active ones are few,[4] and new avenues for the construction of this useful scaffold are requested.

The Pd-catalyzed asymmetric allylic alkylation (AAA) reaction has been widely recognized as a powerful protocol in organic synthesis.[5] Recent progress allows it to install a chiral center at "hard" carbon nucleophiles.[6] The reaction has also been applied successfully in the kinetic resolution. However, the majority of the studies have focused on the resolution of allyl substrates.[7] The resolution of a nucleophile is still very limited. Recently, we succeeded in the kinetic resolution of dihydroindoles and dihydroquinolones via Pd-catalyzed asymmetric allylic amination and allylic alkylation.[8] We disclose the kinetic resolution of 2-substituted 2,3-dihydro-4-pyridones via a Pd-catalyzed AAA reaction. With this strategy, catalytic asymmetric total synthesis of indolizidine (−)-209I was achieved.

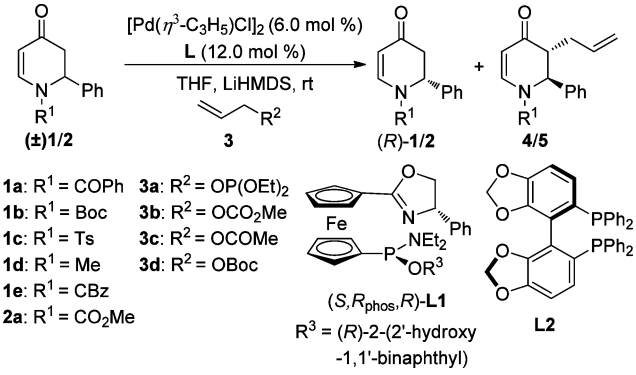
Initially, dihydropyridone **1a** was adopted as prenucleophile in the reaction with allyl reagent **3a** using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and (S,R_{phos},R)-SiocPhox **L1** as the catalyst in the presence of LiHMDS as the base (entry 1, Table1); the allylation product **4a** was afforded in 28% yield and 17% ee while **1a** was recovered in 24% yield and 20% ee. The investigation on the influence of the *N*-substituent of dihydropyridone **1** revealed that the ee and yield were improved when the benzoyl group of **1a** was replaced with the *tert*-butoxycarbonyl (Boc) group (entry 2 vs 1). The kinetic resolution did not take place with *N*-tosyl (Ts) or *N*-methyl dihydropyridone **1** as reactants (entries 3 and 4). The use of *N*-Cbz dihydropyridone **1e** did not lead to good results (entry 5). When dihydropyridone **2a** with a methoxycarbonyl group on nitrogen was used as a prenucleophile, the ee of allylated product **5a** increased to 40% (entry 6). The ee of both recovered **2a** and product **5a** were further improved by using a commercially available chiral ligand (*R*)-SEGPHOS (**L2**) (entry 7). The evaluation of a leaving group in allyl reagents **3** clarified that **3b** with $-OCO_2Me$ as the leaving group was among the best as the ee value of recovered **2a** increased to 70% while that of allylated product **5a** was 67% compared to that using $(EtO)_2PO-$, AcO−, and BocO− as a leaving group (entry 8 vs entries 7, 9, 10). In all cases, the product *trans*-**5a** was obtained, which was determined by ^1H NMR.

To further improve the efficiency of the reaction, the impact of other reaction parameters including bases, solvents, ligands,

Received: February 17, 2014
Published: March 24, 2014

dx.doi.org/10.1021/ol500498m | *Org. Lett.* 2014, 16, 1944−1947

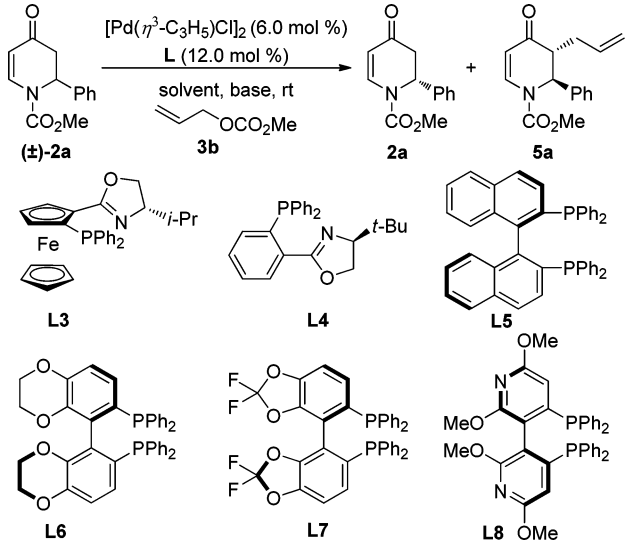
Table 1. Influence of *N*-Substituent and Allyl Reagents on the Kinetic Resolution of 2-Phenyl-2,3-dihydro-4-pyridone[a]



entry	substrate	yield[b] (% 1/2)	ee[c] (%)	product	yield[b] (% 4/5)	ee[c] (%)
1	**1a**	24	20	**4a**	28	17
2	**1b**	45	30	**4b**	46	22
3	**1c**	complex	nd[e]	**4c**	complex	nd[d]
4	**1d**	>98	nd[e]	**4d**	trace	nd[d]
5	**1e**	23	21	**4e**	43	35
6	**2a**	55	31	**5a**	37	40
7	**2a**	48	61	**5a**	22	56
8[e]	**2a**	40	70	**5a**	49	67
9[f]	**2a**	39	31	**5a**	46	28
10[g]	**2a**	48	63	**5a**	45	53

[a]Conditions: molar ratio **1**/**3a**/$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**L**/base = 200:100:6:12:200; **L1** used for entries 1–5, and **L2** used for entries 6–9. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Not determined. [e]**3b** used as allyl reagent. [f]**3c** used as allyl reagent. [g]**3d** used as allyl reagent.

Table 2. Optimization of Reaction Parameters for Kinetic Resolution of 2,3-Dihydro-4-pyridone 2a[a]



				2a		5a	
entry	L	solvent	base	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[c]
1	**L2**	THF	LiHMDS	40	70	49	67
2	**L2**	THF	NaHMDS	nd[d]	nd[d]	trace	nd[d]
3	**L2**	THF	KHMDS	47	2	40	6
4	**L2**	THF	*t*-BuOLi	40	4	39	2
5	**L2**	ether	LiHMDS	42	3	32	3
6	**L2**	toluene	LiHMDS	27	11	33	22
7	**L2**	DCE	LiHMDS	23	8	20	13
8	**L2**	DME	LiHMDS	46	4	32	7
9	**L3**	THF	LiHMDS	37	2	38	2
10	**L4**	THF	LiHMDS	60	10	10	26
11	**L5**	THF	LiHMDS	62	22	35	18
12	**L6**	THF	LiHMDS	26	19	45	17
13	**L7**	THF	LiHMDS	34	49	50	44
14	**L8**	THF	LiHMDS	31	79	45	69
15[e]	**L8**	THF	LiHMDS	48	52	41	75
16[f]	**L8**	THF	LiHMDS	50	67	43	82

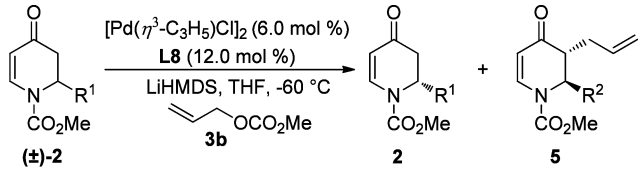
[a]Conditions: molar ratio of **2a**/**3b**/$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**L**/base = 200:100:6:12:200. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Not determined. [e]Reaction was carried out at −20 °C. [f]Reaction was carried out at −60 °C.

and reaction temperature was investigated using **2a** as the substrate and **3b** as the reagent (Table 2). The allylated product **5a** was obtained in 49% yield and 67% ee and the recovered **2a** in 40% yield and 70% ee using LiHMDS as the base (entry 1). In contrast, only a trace of allylated product **5a** was afforded if NaHMDS was the base (entry 2). Employing KHMDS or *t*-BuOLi as base led to the significant decrease in the ee value of both **2a** and **5a** (entries 3 and 4). The screen of solvents revealed that THF was the choice among the solvents, including ether, 1,2-dichloroethane (DCE), dimethoxyethane (DME), and toluene (entry 1 vs entries 5–8). A dramatic variation in enantioselectivity was observed when different chiral *P,N*- and *P,P*-ligands including FcPHOX **L3**, PHOX **L4**, (*R*)-BINAP (**L5**), (*R*)-SYNPHOS (**L6**), (*R*)-Difuorophos (**L7**), and (*S*)-P-PHOS (**L8**) were examined (entries 9–14). It was found that *P,N*-ligands **L3** and **L4** gave unsatisfactory enantioselectivity (entries 9, 10) while bisphosphine ligands showed different behavior. (*R*)-SEGPHOS (**L2**) gave higher values than (*R*)-BINAP (**L5**), (*R*)-SYNPHOS (**L6**), and (*R*)-Difuorophos (**L7**) did in terms of enantioselectivity (entry 1 vs entries 11–13). Gratifyingly, better results were provided by using (*S*)-P-PHOS (**L8**) compared to (*R*)-SEGPHOS (**L2**) (entry 1 vs 14).[9] The enantioselectivity was further improved when the reaction run at lower temperature, providing **5a** with 82% ee (43% yield) and **2a** in 67% ee (50% yield) at −60 °C (entry 16 vs 15). When the amount of base was 60 mol % of 2,3-dihydro-4-pyridone, the yield of allylated product decreased significantly.

On the basis of the above optimal conditions, the substrate scope of the kinetic resolution of 2-substituted dihydropyridones **2** with allyl carbonate **3b** was investigated (Table 3). In general, the reaction afforded allylated *trans*-**5** and recovered **2** in high yields with excellent enantioselectivities. The *S*-factor is between 11 and 43. The electron-donating and -withdrawing substituents at the *meta* or *para* position of the 2-aryl group had limited effect on the enantioselectivity of allylated product **5**, as its ee was consistently excellent (entries 1–6). Use of 2-vinyl dihydropyridones **2h** led to allylated product **5h** with 87% ee (entry 8). This additional alkene functional group should facilitate its further elaboration. Notably, 2-alkyl-2,3-dihydro-4-pyridones were suitable substrates to produce the corresponding products in high enantioselectivity (entries 9–12). The reaction's good tolerance for versatile substituents was a solid foundation for the application of the protocol in organic synthesis. However, the enantioselectivity of recovered dihydropyridones **2** was greatly affected by the 2-substituents. Although the aryl group with different substituents did not

dx.doi.org/10.1021/ol500498m | *Org. Lett.* 2014, 16, 1944–1947

Table 3. Substrate Scope for the Kinetic Resolution of 2-Substituted 2,3-Dihydro-4-pyridones[a]



2a: R^1 = C_6H_5, **2b**: R^1 = *m*-MeO-C_6H_4
2c: R^1 = *p*-MeO-C_6H_4, **2d**: R^1 = *p*-Me-C_6H_4
2e: R^1 = *p*-CF_3-C_6H_4, **2f**: R^1 = *p*-Ph-C_6H_4
2g: R^1 = 2-Naphthyl , **2h**: R^1 = CH=CH_2
2i: R^1 = Cyclohexyl, **2j**: R^1 = CH_2CH_3
2k: R^1 = $CH(CH_3)_2$, **2l**: R^1 = $(CH_2)_3OBn$

		2		5		
entry	substrate	yield%[b]	ee (%)[c]	yield%[b]	ee (%)[c]	*S*[d]
1	**2a**	50	67	43	81	20
2	**2b**	40	49	36	85	20
3	**2c**	41	62	40	89	33
4	**2d**	42	68	35	91	43
5	**2e**	42	77	39	84	27
6	**2f**	57	43	31	93	42
7	**2g**	37	86	43	73	17
8	**2h**	52	48	36	87	23
9	**2i**	32	85	33	83	29
10	**2j**	40	88	42	79	24
11	**2k**	40	41	44	79	14
12	**2l**	46	40	35	77	11

[a]Molar ratio of **2**/**3b**/[Pd(η^3-C_3H_5)Cl]$_2$/**L8**/LiHMDS = 200:100:6:12:200. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Calculated by the method described by Kagan.[7b]

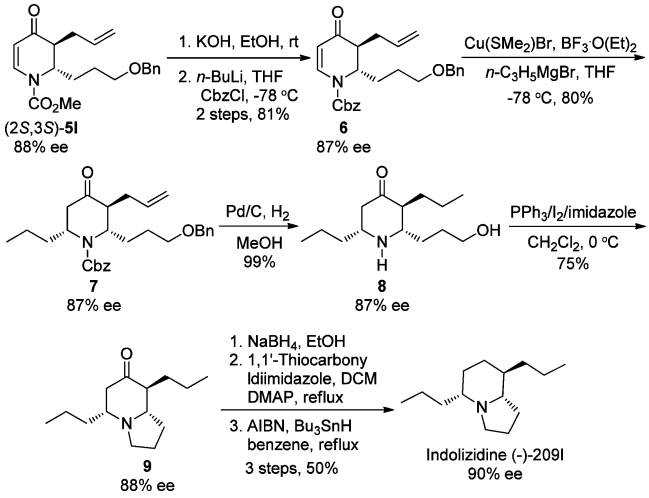
influence the enantioselectivity very much (entries 1 and 3−5), the ee values of recovered **2** were a little bit lower for the reaction of 2-phenyl dihydropyridones with *m*-MeO and *p*-phenyl as the substituent (entries 2 and 6). The reaction also afforded recovered **2** in moderate ee with vinyl, isopropyl, and benzoxypropyl as the substituent (entries 8 and 11−12).

The absolute configuration of the recovered 2-phenyl-2,3-dihydro-4-pyridone (**2a**) was determined to be *R* by removing its methoxycarbonyl group under basic conditions and then comparing the sign of the optical rotation of the resulted product with that reported in literature.[10] Accordingly, the absolute configuration of allylated product **5a** is 2*S*,3*R*.

Indolizidine (−)-209I is an alkaloid found in poisonous frog skin.[11a,b] Several groups have accomplished the synthesis of indolizidine (−)-209I.[11] Enders et al. first realized the synthesis of indolizidine (−)-209I relying on the chemistry of the chiral pyrrolidine hydrazone.[11d] Ma's synthesis features a formal [4 + 2] cycloaddition between an optically pure 3-chloropropylamine and a substituted propiolic acid ester to construct the piperidine core.[11e] Charette employed a Grob fragmentation of chiral aza-bicyclo[2.2.2]octene as the key step for the synthesis of (−)-209I.[11f] All these syntheses rely on the use of enantiopure substances. An enantioselective synthesis of indolizidine (−)-209I based on a catalytic asymmetric strategy is unknown.

To synthesize indolizidine (−)-209I, (2*S*,3*S*)-**5l** was prepared by kinetic resolution of racemic compound **2l** using (*R*)-P-PHOS as the ligand. When the reaction of **2l** with 35 mol % of **3b** was performed in the presence of [Pd(η^3-C_3H_5)Cl]$_2$ and (*R*)-P-PHOS at 4.0 mmol scale, (2*R*,3*S*)-**5l** was obtained in 36% yield with 88% ee. The protective group of (2*R*,3*S*)-**5l** was replaced with the easily removable benzyloxycarbonyl (Cbz) group via a two-step reaction sequence (Scheme 1).[12] The

Scheme 1. Enantioselective Total Synthesis of Indolizidine (−)-209I



resulting compound **6** was subjected to a Cu-catalyzed 1,4-addition to deliver compound **7** with 87% ee in 80% yield.[13] Deprotection of Cbz and the benzyl group and reduction of the double bond of **7** using a catalytic amount of Pd/C under 1 atm of H_2 afforded **8** in quantitative yield. Subsequent cyclization of compound **8** in the presence of Ph_3P/I_2/imidazole gave tricyclic compound **9** with 88% ee.[11e] The ketone functionality of compound **9** was reduced cleanly using $NaBH_4$ followed by an esterification to provide thiocarbamate with thiocarbonyl diimidazole and DMAP. Finally, the resulting thiocarbamate underwent a stannane-mediated radical reduction[14] to afford indolizidine (−)-209I with 90% ee ($[\alpha]^{20}_D$ = −89.5° (1.0, $CHCl_3$), lit $[\alpha]^{22}_D$ = −92.1° (1.0, $CHCl_3$)[11e]). Its NMR data were well matched with those reported.[11d−f] The overall yield is 24% starting from (2*R*,3*S*)-**5l** in an eight-step process.

In summary, we have realized the kinetic resolution of 2-substituted-dihydro-4-pyridones via Pd-catalyzed AAA reaction, providing both 2,3-disubstituted-dihydro-4-pyridones and recovered substrates in high yields and enantioselectivities. With this methodology, the catalytic asymmetric total synthesis of alkaloids indolizidine (−)-209I was accomplished.

■ ASSOCIATED CONTENT

Supporting Information

General procedure for Pd-catalyzed kinetic resolution of **2** and enantioselective synthesis of indolizidine (−)-209I, NMR and HPLC spectra of compounds **2**, **5**−**9**, and indolizidine (−)-209I. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Major Basic Research Development Program (2010CB833300), National Natural Science Foundation of China (21121062, 21272251, 21032007), the Chinese Academy of Sciences, the Technology Commission of Shanghai Municipality and the Croucher Foundation of Hong Kong. This paper is dedicated to Professor Li Xin Dai on the occasion of his 90th birthday.

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(9) For results with other chiral ligands, please see Supporting Information.

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