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Development of a One-Pot Asymmetric Azaelectrocyclization Protocol: Synthesis of Chiral 2,4-Disubstituted 1,2,5,6-Tetrahydropyridines

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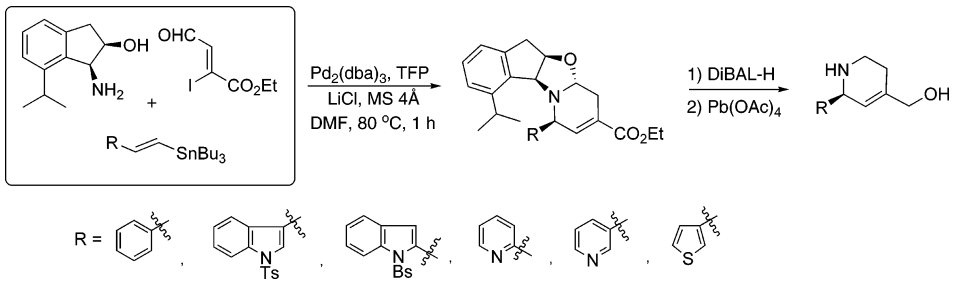
ABSTRACT



A one-pot procedure for tetracyclic chiral aminoacetals, the useful precursors for substituted piperidine synthesis, has been established via Stille–Migita coupling, 6π-azaelectrocyclization, and aminoacetal formation from readily prepared vinylstannanes, vinyliodides, and *cis*-aminoindanol derivatives. Based on the method, chiral 2,4-disubstituted 1,2,5,6-tetrahydropyridines, bearing a variety of aromatic substituents at the C-2 position, have been prepared.

Multicomponent asymmetric tandem, cascade, and one-pot protocols enable rapid access to chiral compounds by simultaneously mixing three or more reactants and/or reagents. Because such protocols significantly reduce experimental operations including tedious isolation procedures for each reaction, much effort has been nowadays devoted to the development of new tandem reactions and the conversion of already existing multistep syntheses into the one-pot procedures. To date, a number of powerful one-pot asymmetric reactions have been reported.[1]

Recently, we developed highly stereoselective asymmetric 6π-azaelectrocyclization of conformationally flexible linear 1-azatrienes using 7-alkyl-substituted *cis*-aminoindanol derivatives.[2−4] Our asymmetric azaelectrocyclization is based on the discovery that the remarkable frontier-orbital interaction between the HOMO and LUMO of 1-azatrienes significantly accelerates azaelectrocyclization in the presence of C4-carbonyl and C6-alkenyl or aryl substituents.[5,6] Based on the method, chiral tetrahydropyridine derivatives have been successfully produced with high yields and selectivity. To establish asymmetric 6π-azaelectrocyclization toward a

(1) The importance of asymmetric multicomponent reactions involving the tandem and the domino processes has drawn much attention, see review: (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. For recent examples, see: (c) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Domling, A. *Org. Lett.* **2003**, *5*, 4021. (d) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2004**, *45*, 6637. (e) Timmer, M. M. S.; Risseeuw, P. M. D.; Filippov, D. V.; Plaisier, J. R.; Marel, G. A.; Overkleeft, H. S.; Boom, J. H. *Tetrahedron: Asymmetry* **2005**, *15*, 177. (f) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575. (g) Marigo, M.; Schulte, T.; Franzen, J.; Jorgensen, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 15710.

(2) (a) Tanaka, K.; Katsumura, S. *J. Am. Chem. Soc.* **2002**, *124*, 9660. (b) Tanaka, K.; Kobayashi, T.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 5906.

(3) Kobayashi, T.; Tanaka, K.; Miwa, J.; Katsumura, S. *Tetrahedron: Asymmetry* **2004**, *15*, 185.

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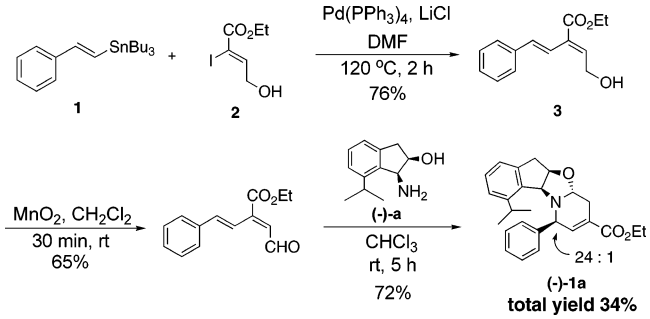
new strategy for alkaloid synthesis, however, operation, scale-up, and substrate preparation for the electrocyclization of our previous method had to be reinvestigated. Herein, we report a one-pot asymmetric 6π-azaelectrocyclization procedure and its application to the new stereoselective synthesis of chiral 2,4-substituted tetrahydropyridines[7] that bear various aromatic substituents at the C-2 position.

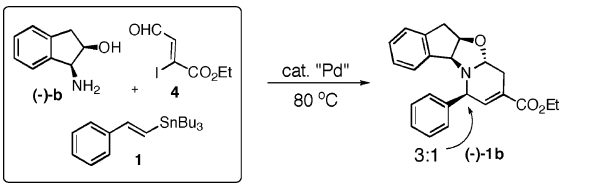
Previously we reported the synthesis of tetracyclic 2,4-disubstituted tetrahydropyridine (−)-**1a**,[2,3] a promising precursor for the preparation of substituted piperidine derivatives, in 34% yield in three steps, as shown in Scheme 1. The sequence involves the following steps: (1) Stille−Migita coupling of vinyl stannane **1** with vinyl iodide **2**; (2) oxidation of resulting allylic alcohol **3** by manganese dioxide; and (3) reaction with (−)-7-isopropyl *cis*-1-amino-2-indanol (−)-**a**, resulting in highly stereoselective azaelectrocyclization, followed by aminoacetal formation.

Scheme 1. Previous Asymmetric 6π-Azaelectrocyclization Method toward Chiral Piperidines



To achieve practical application of our asymmetric azaelectrocyclization method for natural alkaloid synthesis, we investigated a tandem one-pot procedure as an effective preparation method by mixing three components of (*E*)-vinyl stannane **1**, *cis*-2-iodopropanal **4**, and (−)-*cis*-1-amino-2-indanol (−)-**b** in the presence of a palladium catalyst (Table 1). Although aminoindanol (−)-**b** was expected to show the moderate stereoselectivity of azaelectrocyclization, we first used this commercially available amine to optimize the one-pot procedures.

Table 1. Optimization of One-Pot Azaelectrocyclization



entry	catalyst	additive	solvent	time	yield
1	$Pd(PPh_3)_4$	LiCl	DMF	2 h	28%
2	$Pd(PPh_3)_4$	LiCl	DMSO	4 h	12%
3	$Pd(PPh_3)_4$	LiCl	DMSO, THF	3.5 h	22%
4	$Pd(PPh_3)_4$		DMF	8 h	0%
5	$Pd(PPh_3)_4$	CuI	DMF	7.5 h	*a*
6	$Pd(PPh_3)_4$	CuI, LiCl	DMF	20 min	10%
7	$Pd(CH_3CN)_2Cl_2$	LiCl	DMF	1 h	55%
8	$Pd_2(dba)_3$, $P(2\text{-furyl})_3$	LiCl	DMF	1 h	70%
9	$Pd_2(dba)_3$, $P(2\text{-furyl})_3$	LiCl Mg_2SO_4	DMF	1 h	55%
10	$Pd_2(dba)_3$, $P(2\text{-furyl})_3$	LiCl MS 4 Å	DMF	1 h	82%

[a] Corresponding pyridine was produced.

For the first trial, (*E*)-vinyl stannane **1** and vinyl iodide **4** were initially subjected to Stille coupling and, subsequently, *cis*-aminoindanol (−)-**b** was added to the reaction mixture to affect Schiff base formation, followed by 6π-azaelectrocyclization. However, the reaction between **1** and **4** in the presence of 5 mol % of $Pd(PPh_3)_4$ in dimethylformamide at 80 °C provided complex mixtures. Therefore, first vinyl iodide **4** and aminoindanol (−)-**b** were mixed and expected to give a more stable protected aminoacetal (vide infra) that would successfully participate in Stille coupling with stannane **1**, followed by tandem azaelectrocyclization. To our delight, using this procedure, the desired tetracyclic compound (−)-**1b** was obtained in 28% yield with 3:1 diastereoselectivity (Table 1, entry 1). Further examination of the solvents, additives, and Pd(0) catalysts led to the following informative observations: (i) DMF is a suitable solvent (Table 1, entries 1−3); (ii) as an additive, LiCl increases product yields (Table 1, entries 1, 4−6); (iii) $Pd_2(dba)_3$/trifurylphosphine system is the optimal Pd(0) catalyst (Table 1, entries 1, 7, and 8);[8,9] and (v) MS $4A^0$ might efficiently trap the H_2O produced during aminoacetal formation, improving the Stille coupling efficiency (Table 1, entries 1, 9, and 10). Finally, the combination of optimized conditions found in Table 1 led to (−)-**1b** in 82% yield and 3:1 diastereoselectivity, namely, by using the $Pd_2(dba)_3$/trifurylphosphine catalyst in the presence of LiCl and MS $4A^0$ in DMF at 80 °C (Table 1, entry 10).

After establishing the optimal one-pot procedure, we then examined the stereoselectivity of azaelectrocyclization. Diastereoselectivity was significantly improved by applying

(4) Most recently, Hsung and co-workers also reported asymmetric azaelectrocyclization, see: (a) Wei, L.-L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145. (b) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei. L.-L.; Gerasyuto, A. I.; Brennessel, W. W. *J. Am. Chem.* Soc. **2002**, *124*, 10435. (c) Sydorenko, N.; Hsung, R. P.; Vera, E. L. *Org. Lett.* **2006**, *8*, 2614.

(5) (a) Tanaka, K.; Mori, H.; Fujii, S.; Ikeda, M.; Itagaki, Y.; Katsumura, S. *Tetrahedron Lett.* **1998**, *39*, 1185. (b) Tanaka, K.; Kamatani, M.; Mori, H.; Fujii, S.; Ikeda, K.; Hisada, M.; Itagaki, Y.; Katsumura, S. *Tetrahedron* **1999**, *55*, 1657. (c) Tanaka, K.; Katsumura, S. J. *Synth. Org. Chem. Jpn.* **1999**, *57*, 876.

(6) (a) Tanaka, K.; Katsumura, S. *Org. Lett.* **2000**, *2*, 373. (b) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099.

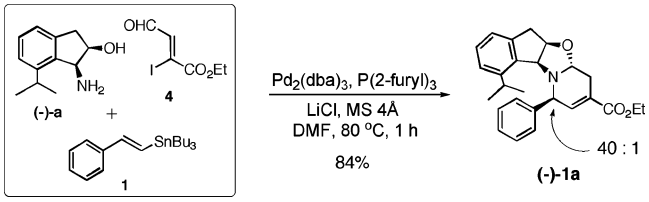
(7) There are several reports on the stereoselective synthesis of chiral tetrahydropyridines, see: (a) Huang, H.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 626. (b) Timen, A. S.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 9958. (c) Ramachandaran, P. V.; Burghatdt, T. E.; Bland-Berry, L. *J. Org. Chem.* **2005**, *70*, 7911. (d) Lemire, A.; Beaudoin, D.; Grenon, M.; Charettam, A. B. *J. Org. Chem.* **2005**, *70*, 2368. (e) Lemire A.; Charettam, A. B. *Org. Lett.* **2005**, *7*, 2747. (f) Yamada, S.; Jahan, I. *Tetrahedron Lett.* **2005**, *46*, 8673.

(8) Farina, V.; Krishnaurthy, V.; Scott, W. J. *The Stille Reaction*; John Wiley & Sons: New York, 1998.

(9) (a) Langli, G.; Gundersen, L.-L.; Rise, F. *Tetrahedron* **1996**, *52*, 5625. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

isopropyl-substituted aminoindanol (−)-**a**, a chiral amine previously developed for kinetically controlled asymmetric azaelectrocyclization with general aldehydes (Scheme 2).[2]

Scheme 2. One-Pot Azaelectrocyclization Using (−)-**7**-*iso*-Propyl-*cis*-1-amino-2-indanol



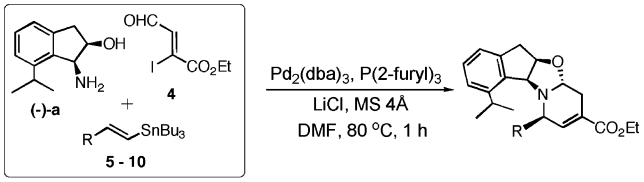
Thus, corresponding tetrahydropyridine (−)-**1a** was obtained in 84% yield with an almost single isomer (40:1 by ^{1}H NMR analysis). Note that this one-pot procedure successfully created four new bonds simultaneously and produced better results than the previously developed stepwise procedure[5] shown in Scheme 1 (84% and 40:1 for the one-pot protocol vs 34% and 24:1 for the stepwise method).[10]

The developed one-pot asymmetric azaelectrocyclization procedure was applied to various aromatic substituents at the C-2 position of the tetrahydropyridines (Table 2). Thus, a small chiral tetrahydropyridine library bearing indolyl (Table 2, entries 1 and 2), quinolyl (Table 2, entry 3), pyridyl (Table 2, entries 4 and 5), and thienyl derivatives (Table 2, entry 6) was successfully prepared. Note that all tetracyclic heterocycles could be efficiently obtained with high diastereoselectivity ranging from 12:1 to 18:1 with satisfactory yields (67−80%).

Finally, removal of the indanol moiety of the tetracyclic compound was examined (Table 3). According to our previously reported method,[2] aminoacetal compounds were first reduced by lithium aluminum hydride, and the resulting diols were treated by manganese dioxide as a mild oxidant. However, in some cases, chemical yields were very low for each step, and the procedures could not be reproduced. After re-examining the reduction/oxidation conditions, we found that using diisobutylaluminum hydride (DIBAL-H) and lead tetraacetate treatment resulted in the clean removal of the hydroxy indane moiety (Table 3). Cyclic aminoacetal compounds were treated with DIBAL-H at −78 °C to provide corresponding diols in 69−87% yield. They were oxidized by lead tetraacetate[11] in the presence of *n*-propylamine[12] at −50 °C to afford the corresponding amino alcohol in 79−91% yields, except for one case, (−)-**8a** (29%, Table 3, entry 5). Thus, a synthetically practical route for chiral 2,4-disubstituted tetrahydropyridines has been established.

A possible mechanism for the established one-pot procedure is shown in Figure 1. First, in situ formation of cyclic aminoacetal **18** from aldehyde **4** and aminoindanol (−)-**a**, has been admitted by ^{1}H NMR analysis. This aminoacetal formation protects the unstable aldehyde moiety in **4**, thus successfully achieving the subsequent Stille−Migita coupling

Table 2. One-Pot Azaelectrocyclization Utilizing Variously Substituted Vinyl Stannanes with Heterocycles



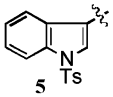
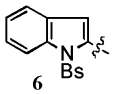
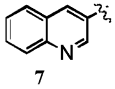
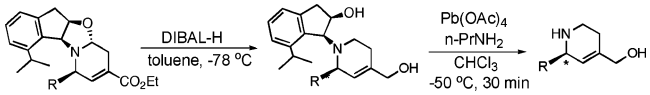
entry	R	product	yield	dr (at 2-position)
1	 **5**	**(-)-5a**	72%	> 16 : 1
2	 **6**	**(-)-6a**	67%	> 12 : 1
3	 **7**	**(-)-7a**	68%	> 15 : 1
4	 **8**	**(-)-8a**	80%	> 16 : 1
5	 **9**	**(-)-9a**	78%	> 17 : 1
6	 **10**	**(-)-10a**	74%	> 15 : 1

Table 3. Removal of Indanol Auxiliary



entry	substrate	product	yield of diol	yield of amino alcohol
1	(−)-**1a**	(−)-**11**	87	87
2	(−)-**5a**	(−)-**12**	80	91
3	(−)-**6a**	(−)-**13**	75	93
4	(−)-**7a**	(−)-**14**	71	84
5	(−)-**8a**	(−)-**15**	84	29
6	(−)-**9a**	(−)-**16**	69	79
7	(−)-**10a**	(−)-**17**	85	84

(10) We postulated that the one-pot procedure at 80 °C would produce more thermodynamically stable products with excellent diastereoselectivity, while the previously reported kinetically controlled azaelectrocyclization at room temperature[4] produced the same major products. The same outcome of azaelectrocyclization diastereoselectivity for both cases could be explained by considering the transition state of electrocyclization and the stable conformer of the products, such as (−)-**2a**. Further details will be provided in the full account.

(11) Suginome, H.; Umeda, H.; Masamune, T. *Tetrahedron Lett.* **1970**, *11*, 4571.

(12) In the absence of *n*-propylamine conditions, yields were low. *n*-Propylamine maintained a basic condition and probably caught the resulting dialdehyde from $Pb(Ac)_4$ oxidation, followed by aqueous work up.

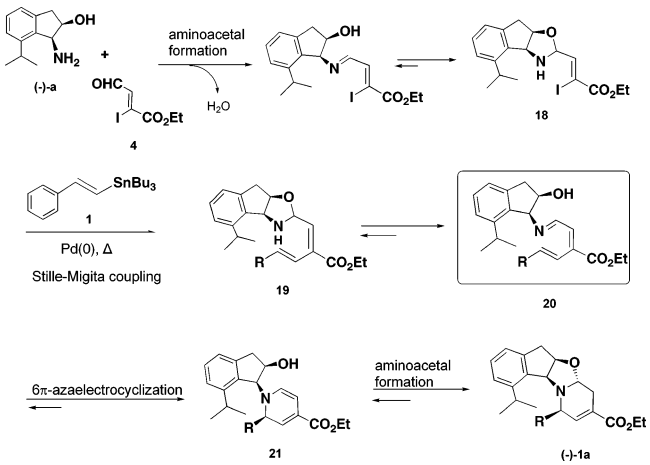


Figure 1. Possible mechanism leading to (−)-**1a** by one-pot azaelectrocyclization.

with vinyl stannane **1**. Coupling product **19** is in equilibrium with 1-azatriene **20**, which spontaneously cyclizes into the corresponding dihydropyridine **21**. The reactive enamine moiety in **21** is then trapped by the proximal hydroxyl group of *cis*-aminoindanol, giving rise to the observed product, (−)-**1a**.

In summary, we achieved efficient chiral tetrahydropyridine synthesis by one-pot tandem 6π-azaelectrocyclization. The reaction proceeds by simply mixing the four components in the following order: vinyl iodide, *cis*-aminoindanols, palladium catalyst, and vinyl stannanes. By applying the developed one-pot protocol, a small 2,4-disubstituted tetrahydropyridine library, which contains various heterocycles at the C-2 position, was efficiently prepared. Note that these heterocycles, which substituted chiral tetrahydropyridines, are not readily accessible by the previous existing method. An application of the current one-pot azaelectrocyclization for piperidine alkaloid synthesis will be disclosed in the following account.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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