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Kinetic Resolution of 2,3-Dihydro-2-substituted 4-Quinolones by Palladium-Catalyzed Asymmetric Allylic Alkylation

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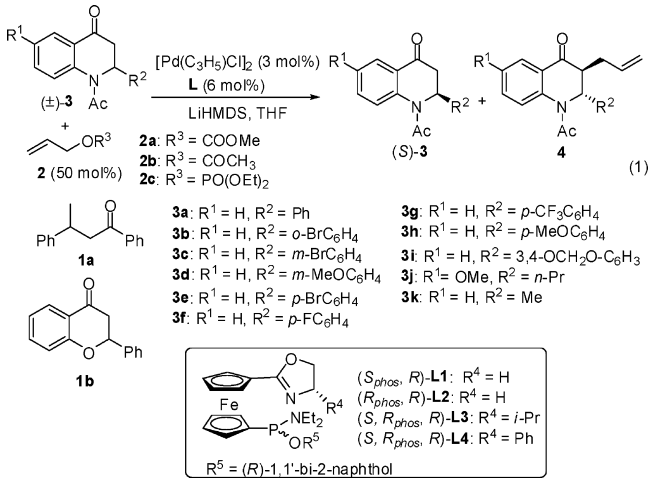
Kinetic resolution as one of the most powerful tools in asymmetric catalysis has found wide applications in both academies and industry.[1] Many procedures have been developed with a high ee value and yield, for both products and recovered starting materials. However, the reactions suitable for the kinetic resolution are still limited. Only in a few examples, a new chiral center in addition to that present in the starting material was created in products.[2] There is much yet to be explored in relation to kinetic resolution. On the other hand, Pd-catalyzed asymmetric allylic alkylation reactions have been widely recognized as a powerful protocol in organic synthesis.[3] Recent progress allows it to install a chiral center at "hard" carbon nucleophiles.[4,5] The Pd-catalyzed allylic substitution reactions have also been applied successfully in the kinetic resolution; however, the majority of studies focus on the resolution of allyl substrates.[6] The resolution of a nucleophile is still very limited.[7] Recently, we succeeded in the kinetic resolution of dihydroindoles via Pd-catalyzed asymmetric allylic amination.[7] Here, we report preliminary results on the highly efficient kinetic resolution of "hard" carbon nucleophiles, 2,3-dihydro-2-substituted 4-quinolones, by Pd-catalyzed AAA reaction. The application of the methodology in organic synthesis is also demonstrated.



To test our idea, ketones **1a** and **1b** were adopted as prenucleophile in the reaction with allyl reagent **2a** using $[Pd(C_3H_5)Cl]_2$ and (*S*, R_{phos}, *R*)-SiocPhox **L3** as catalyst in the presence of LiHMDS as base (eq 1). An allylation product with low yield and ee was obtained for ketone **1a**, while a retro-Michael addition reaction took place for ketone **1b**. Delightfully, the allylation product **4a** in 46% yield and 73% ee was afforded while **3a** was recovered in 40% yield and 71% ee when 2,3-dihydro-2-phenyl-4-quinolone **3a** was used as prenucleophile. It is noteworthy that the adduct **4a** incorporates chiral centers at both α and β positions of ketone. This procedure represents a novel route to such a structural motif in contrast to the arduous asymmetric synthesis through conventional processes.[8] The recovered optically active **3a** is also of interest with its prominent feature as biologically active molecules.[9]

Table 1. Optimization of Parameters for the Reaction of **3a** with **2**[a]

			3		4		
entry	2	L	yield%[b]	ee%[c]	yield%[b]	ee%[c]	d.r.[d]
1	**2a**	**L3**	40	71	46	73	10/1
2	**2a**	**L1**	53	5	27	27	13/1
3	**2a**	**L2**	32	47	26	79	8/1
4	**2a**	**L4**	40	83	41	71	17/1
5	**2a**	**L5**[e]	40	11	34	13	50/1
6	**2a**	**L6**[e]	42	9	39	13	9/1
7	**2a**	**L7**[e]	19	5	23	13	20/1
8	**2a**	**L8**[e]	35	0	49	−25[f]	11/1
9	**2b**	**L4**	26	59	24	49	18/1
10	**2c**	**L4**	32	93	45	65	8/1
11[g]	**2c**	**L4**	26	95	24	73	17/1
12[h]	**2c**	**L4**	37	99	49	79	>99/1
13[i]	**2c**	**L4**	45	99	48	93	>99/1
14[i,j]	**2c**	**L4**	51	77	41	53	>99/1
15[i,k]	**2c**	**L4**	46	87	47	87	>99/1

[a] Molar ratio of **3a/2**/$[Pd(C_3H_5)Cl]_2$/**L**/base = 200:100:6:12:200. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR. [e] **L5** = (*R*)-BINAP, **L6** = (*S*)-*tert*-BuPHOX, **L7** = (*S*, S_p)-*iso*-PrFcPHOX, **L8** = (*R*, *R*)-DACH-phenyl Trost ligand. [f] The reversed sequence of peaks by HPLC. [g] Run at −5 °C. [h] Run at −30 °C. [i] Run at −50 °C. [j] Ac of **3a** was replaced with H. [k] Ac of **3a** was replaced with Boc.

Encouraged by these results, the impact of the reaction parameters on the efficiency of the reaction was investigated (Table 1). The choice of substituent on the oxazoline ring and the combination of chiral elements in ligands are important. Much lower ee was obtained in the presence of (S_{phos}, *R*)-**L1** rather than (R_{phos}, *R*)-**L2** (entry 2 vs 3), suggesting the chiralities in the latter is matched. We then probed the influence of the substituent on the oxazoline ring in SiocPhox ligands and found (*S*, R_{phos}, *R*)-**L4** with Ph as the substituent gave the best results, affording **4a** with 71% ee in 41% yield, with recovered **3a** in 83% ee and 40% yield (entry 4 vs 1). Several commercially available chiral ligands including (*R*)-BINAP, (*S*)-*tert*-BuPHOX, (*S*, S_p)-*iso*-PrFcPHOX, and (*R*, *R*)-DACH-phenyl Trost ligand were also examined; nevertheless, only low ee was acquired (entries 5−8). Evaluation of the leaving group in allyl reagents **2** clarified that phosphate was among the best as the ee value of the recovered **3a** increased from 83% and 59% to 93% (entry 10 vs 4, 9). Gratifyingly, enantioselectivity increased dramatically when the reaction proceeded at lower temperature, providing **4a** with 93% ee (48% yield) and **3a** in 99% ee (45% yield) at −50 °C, while lower ee value was obtained for both **4a** and **3a** at −30 °C (entry 13 vs 12). The substituent on the nitrogen of **3**

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also played a role in the reaction. When the acetyl group of **3a** was replaced by H or Boc, the ee of both recovered substrates and allylated products decreased greatly (entries 14, 15 vs 13). The screen of solvents and bases revealed that THF and LiHMDS were the best choice (not showed in Table 1 but see Supporting Information).

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

		3		4		
entry	substrate	yield%[b]	ee (%)[c]	yield%[b]	ee (%)[c]	S[d]
1	**3a**	45	99	48	93	145
2	**3b**	43	99	38	83	56
3	**3c**	44	96	47	91	83
4	**3d**	44	98	42	93	127
5[e]	**3e**	46	99	38	90	99
6	**3f**	42	99	48	91	111
7	**3g**	47	99	49	93	145
8	**3h**	46	99	49	91	111
9	**3i**	46	99	46	90	99
10	**3j**	41	93	37	89	58
11[f]	**3k**	37	87	46	87	40

[a] Reaction conditions: **3/2c**/[Pd(C_3H_5)Cl]$_2$/**L4**/base = 100:200:6:12:200, 0.05 M of 3 in THF at −50 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Calculated by the method describe by Kagan.[1a] [e] d.r. of **4e** is 13/1. [f] d.r. of **4k** is 5/1.

The substrate scope was examined, and the results were compiled in Table 2 under the above optimized conditions. Generally, the reactions provided allylated products **4** with *trans*-stereoselectivity in 37−49% yields and 83−93% ee accompanied with 37−47% yields of recovered starting materials in 87−99% ee (*S*-factor is 40−145). The substituents on both the 2,3-dihydro-4-quinolone core and 2-phenyl group had limited effect on the enantioselectivity of recovered **3** as its ee was consistently excellent (entries 1−9). The substituents on the 2-phenyl group exerted some impact on the selectivity of allylated products **4**. When the substituent was at the *ortho*-position of the 2-phenyl group, the stereoselectivity is slightly low, giving **4b** in 83% ee and 38% yield, presumably due to the steric hindrance (entry 2). While either an electron-donating or -withdrawing group was at the *meta*- and *para*-position of the 2-phenyl group, allylated products **4** were furnished with excellent ee (entries 3−9). Notably, the reaction of 2-alkyl-2,3-dihydro-4-quinolones gave excellent enantioselectivity (entries 10 and 11), while the diastereoselectivity of **4k** decreased to 5/1 (entry 11).

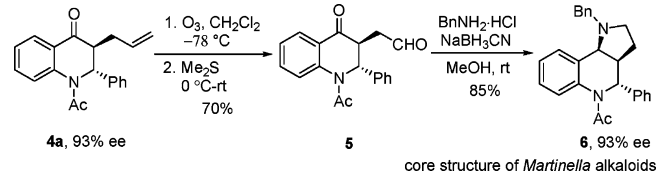
This kinetic resolution proceeded even on gram-scale under mild conditions with high efficiency. Treatment of 1.17 g of **3a** with 0.43 g of **2c** under the above conditions still furnished a 44% yield of **4a** in 93% ee and 46% yield of **3a** in 99% ee.

The absolute configuration of the recovered 2,3-dihydro-2-phenyl-4-quinolone **3a** was determined as (*S*) by removing its acetyl group under basic conditions and comparing the sign of the optical rotation of the product with that reported by literature.[10] Accordingly, the allylated **4a** has the (2*R*,3*S*) configuration.

Allylated product **4a** was easily converted into pyrrolo[3,2-*c*]quinoline **6** without the loss of optical activity through ozonolysis and reduction followed by reductive amination. It is noticeable that compound **6** is the core structure of biologically active *Martinella* alkaloids[11a] and reported compounds having tachykinin receptor antagonistic activity.[11b] Its structure was unequivocally confirmed by its X-ray diffraction analysis, which also provides evidence to support the *trans*-stereochemistry of **4a**.

The present work realized the success in the kinetic resolution of a carbon nucleophile for the first time via Pd-catalyzed AAA reaction, providing both 2,3-disubstituted 2,3-dihydro-4-quinolones and recovered substrates in high yields and ee. The usefulness of the methodology has been demonstrated. It provided a new approach for application of Pd-catalyzed AAA in organic synthesis. Studies on the extension of the protocol to other carbon nucleophiles and applications of the aforementioned procedure in organic synthesis are in progress.

Scheme 1. Transformation of Allylated Adduct **4a** into Valuable Compound



4a, 93% ee **5** **6**, 93% ee

core structure of *Martinella* alkaloids

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Supporting Information Available: General procedure for kinetic resolution, spectral data for **3a**−**3k** and **4a**−**4k**, and X-ray analysis data of **4c** and **6** (cif file). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For some reviews: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (d) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407. (e) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

(2) For some examples of creating new chiral center via kinetic resolution: (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (b) Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508. (c) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 927. (d) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (e) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244.

(3) For some reviews: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(4) (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (b) Braun, M.; Laicher, F.; Meier, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3494. (c) Weiss, T. D.; Helmchen, G.; Kazmaier, U. *Chem. Commun.* **2002**, 1270. (d) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (e) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (f) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (g) Bélanger, É; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034. (h) Deska, J.; Kazmaier, U. *Angew. Chem., Int. Ed.* **2007**, *46*, 4570. (i) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056.

(5) (a) Yan, X. X.; Liang, C. G.; Zhang, Y.; Hong, W.; Cao, B. X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544. (b) Zheng, W. H.; Zheng, B. H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718. (c) Zhang, K.; Peng, Q.; Hou, X.-L.; Wu, Y. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1741. (d) Liu, W.; Chen, D.; Zhu, X.-Z.; Wan, X.-L.; Hou, X.-L. *J. Am. Chem. Soc.* **2009**, *131*, 8734.

(6) (a) Hayashi, T.; Yamamoto, A.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1090. (b) Choi, Y. K.; Suh, J. H.; Lee, D.; Lim, I. T.; Jung, J. Y.; Kim, M. J. *J. Org. Chem.* **1999**, *64*, 8423. (c) Reetz, M. T.; Sostmann, S. *J. Organomet. Chem.* **2000**, *603*, 105. (d) Longmire, J. M.; Wang, B.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 5435. (e) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237. (f) Hughes, D. L.; Palucki, M.; Yasuda, N.; Reamer, R. A.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 2762. (g) Lüssem, B. J.; Gais, H.-J. *J. Am. Chem. Soc.* **2003**, *125*, 6066. (h) Faller, J. W.; Wilt, J. C.; Parr, J. *Org. Lett.* **2004**, *6*, 1301. (i) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (j) Onitsuka, K.; Matsushima, Y.; Takahashi, S. *Organometallics* **2005**, *24*, 6472. (k) Jiang, X.-B.; Van Leeuwen, P.; Reek, J. *Chem. Commun.* **2007**, 2287.

(7) Zheng, B. H.; Hou, X. L. *Org. Lett.* **2009**, *11*, 1789.

(8) (a) Job, A. C.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253. (b) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132. (c) Zagozda, M.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1958.

(9) (a) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155. (b) Zhang, S.-X.; Feng, J.; Kuo, S.-C.; Brossi, A.; Hamel, E.; Tropsha, A.; Lee, K.-H. *J. Med. Chem.* **2000**, *43*, 167.

(10) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5317.

(11) (a) Lovely, C. J.; Bararinarayana, V. *Curr. Org. Chem.* **2008**, *12*, 1431. (b) U.S. Patent 0 039 452, 2008.

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