Communications

Organocatalysis

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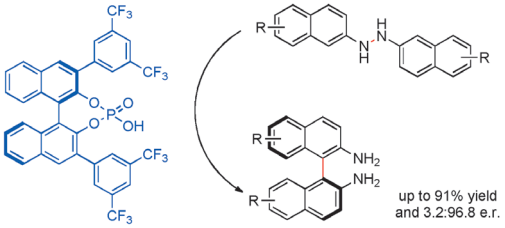
Catalytic Asymmetric Benzidine Rearrangement



A chiral Brønsted acid catalyzes the asymmetric benzidine rearrangement of *N*,*N*′-dinaphthylhydrazines. Different electronically and structurally diverse axially chiral 2,2′-binaphthyl diamine (BINAM) derivatives are obtained with high enantioselectivity.

Organocatalysis

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Catalytic Asymmetric Benzidine Rearrangement**

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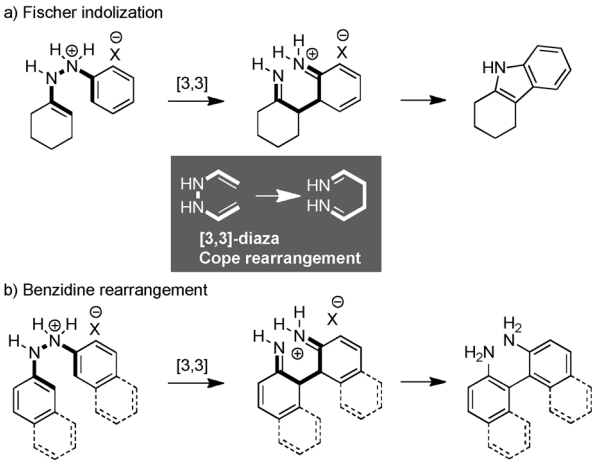
The [3,3]-diaza Cope rearrangement is a powerful synthetic principle that can be utilized to generate a C–C bond at the expense of an N–N bond. It forms the basis of important and fundamental acid-catalyzed transformations such as the Fischer indolization and the benzidine rearrangement (Scheme 1).[1–3] Recently, our group has established the first



Scheme 1. The diaza Cope rearrangement and its synthetic utilization.

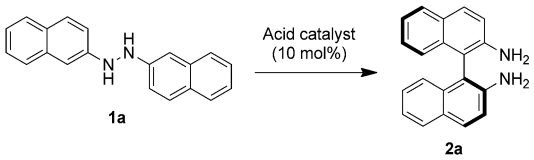
catalytic asymmetric variant of the Fischer indolization.[4] Two years ago, in light of the mechanistic similarities between the two reactions, we set up a program towards developing an asymmetric benzidine rearrangement. Such a transformation may find utility in the synthesis of highly useful chiral biaryls such as 1,1′-binaphthyl-2,2′-diamine (BINAM). Herein we report the successful realization of this idea with a benzidine rearrangement of *N*,*N*′-dinaphthylhydrazines catalyzed by a chiral phosphoric acid, furnishing the corresponding BINAM derivatives with high enantioselectivity.

Although several well-established BINAM-based catalysts have been developed for asymmetric catalysis,[5,6] BINAM is rather expensive and its current synthetic route relies on a classical resolution.[7] Only few synthetic attempts towards enantiopure BINAM derivatives exist. These involve a moderately enantioselective oxidative homocoupling of 2-naphthylamines.[8]

We envisioned that a catalytic enantioselective benzidine rearrangement of *N*,*N*′-dinaphthylhydrazines could potentially be a powerful and general approach towards BINAM derivatives. Previously, only one example of an asymmetric benzidine rearrangement was reported by Sannicolò, using three equivalents of camphor sulfonic acid to obtain the product with poor enantioselectivity.[9,10]

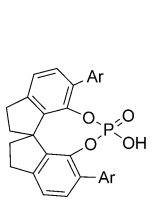
We started our studies by reacting hydrazine **1a** in $CHCl_3$ with different chiral Brønsted acid catalysts.[11,12] Spirocyclic phosphoric acid catalysts (*S*)-**3a** and (*S*)-**3b**, which provided excellent results in our asymmetric Fischer indolization gave product **2a** in 52% and 27% yield, respectively. However, the reaction did not lead to full conversion and the enantioselectivity was poor in both cases (Table 1, entries 1 and 2).

Table 1: Reaction development.[a]

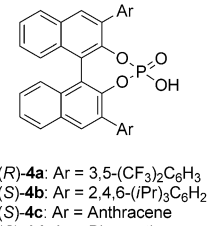


Entry	Catalyst	Solvent	*T* [°C], *t* [h]	Yield [%]	e.r.
1[b]	(*S*)-**3a**	$CHCl_3$	RT, 22	52	60:40
2[b]	(*S*)-**3b**	$CHCl_3$	RT, 48	27	60.1:39.9
3	(*R*)-**4a**	$CHCl_3$	RT, 22	67	17.5:82.5
4	(*S*)-**4b**	$CHCl_3$	RT, 48	51	65.3:34.7
5	(*S*)-**4c**	$CHCl_3$	RT, 48	63	60:40
6[b]	(*S*)-**4d**	$CHCl_3$	RT, 22	51	70:30
7[b]	(*R*)-**4e**	$CHCl_3$	RT, 48	21	23.7:76.3
8[b]	(*S*)-**5**	$CHCl_3$	RT, 48	38	44.3:55.7
9	(*R*)-**4a**	CH_2Cl_2	RT, 24	62	17:83
10	(*R*)-**4a**	PhMe	RT, 24	54	15.5:84.5
11	(*R*)-**4a**	$CHCl_3$	−15, 48	67	9.5:90.5
12[b]	(*R*)-**4a**	PhMe	−15, 48	57	14.8:85.2
13[b]	(*R*)-**4a**	$CHCl_3$	−50, 66	65	5.2:94.8
14[b,c]	(*R*)-**4a**	$CHCl_3$	−50, 66	69	4.5:95.5
15[d]	(*R*)-**4a**	$CHCl_3$	−50, 55	76	4:96
16[b,d,e]	(*R*)-**4a**	$CHCl_3$	−50, 66	67	4:96
17[d,e,f]	(*R*)-**4a**	$CHCl_3$	−50, 48	77	3.5:96.5

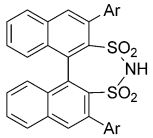
[a] Reactions were run on a 0.05 mmol scale and the e.r. value was determined by using HPLC. [b] Reactions were incomplete. [c] Reactions were run at a concentration of 0.05 M. [d] Reactions were run at a concentration of 0.025 M. [e] Reactions were run with 5 mol% catalyst loading. [f] Reaction was run with 50 mg of CG-50 resin.



(*S*)-**3a**: Ar = 3,5-$(CF_3)_2C_6H_3$
(*S*)-**3b**: Ar = 2,4,6-$(i\text{Pr})_3C_6H_2$



(*R*)-**4a**: Ar = 3,5-$(CF_3)_2C_6H_3$
(*S*)-**4b**: Ar = 2,4,6-$(i\text{Pr})_3C_6H_2$
(*S*)-**4c**: Ar = Anthracene
(*S*)-**4d**: Ar = Phenanthene
(*R*)-**4e**: Ar = $SiPh_3$



(*S*)-**5**: Ar = 3,5-$(CF_3)_2C_6H_3$

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While most investigated binaphthyl-based phosphoric acids gave only moderate results, catalyst (*R*)-**4a** gave product **2a** in promising yield and enantioselectivity (Table 1, entries 3–7). Interestingly, the chiral Brønsted acid catalyst (*S*)-**5**, which is based on a stronger acidic disulfonimide, gave poor conversion as well as a poor e.r. value (entry 8). We therefore selected catalyst (*R*)-**4a** for further optimizations. The evaluation of different solvents (entries 9 and 10) showed that toluene was a comparably effective solvent. However, when performing the reactions at lower temperature (−15 °C), $CHCl_3$ was found to be superior (entries 11 and 12). Lowering the reaction temperature to −50 °C significantly increased the e.r. value to 5.2:94.8 and gave the product in 65 % yield with an incomplete consumption of **1a** after 66 h (entry 13). Interestingly, when the reactions were conducted at that same temperature but with a lower concentration, a beneficial effect on the conversion with virtually no effect on the e.r. value was found (entries 14 and 15). Finally, addition of weakly acidic CG-50 resin as an additive, allowed us to perform the reaction at even lower catalyst loading with full consumption of hydrazine **1a** (entries 16 and 17).

With the optimized conditions established, the scope of the reaction was explored next (Scheme 2). A number of naphthyl hydrazines with electronically diverse substituents at different ring positions yielded the desired products, typically with good yields and enantioselectivities of e.r. > 95:5. Both substrates with substituents at their 6- or 7-position, irrespective of their electronic nature gave the corresponding BINAM derivatives with good yields and high enantioselectivity.

Until today, no generally accepted mechanism of the benzidine rearrangement has been established. There is considerable debate concerning the question, whether the reaction proceeds through a monocationic pathway, involving a structure such as **A**, or through a dicationic, potentially radical-cation-involving pathway via structures **B** or **C** (Figure 1). We hypothesized that a study on the nonlinear effects in the asymmetric catalysis could give an indication,

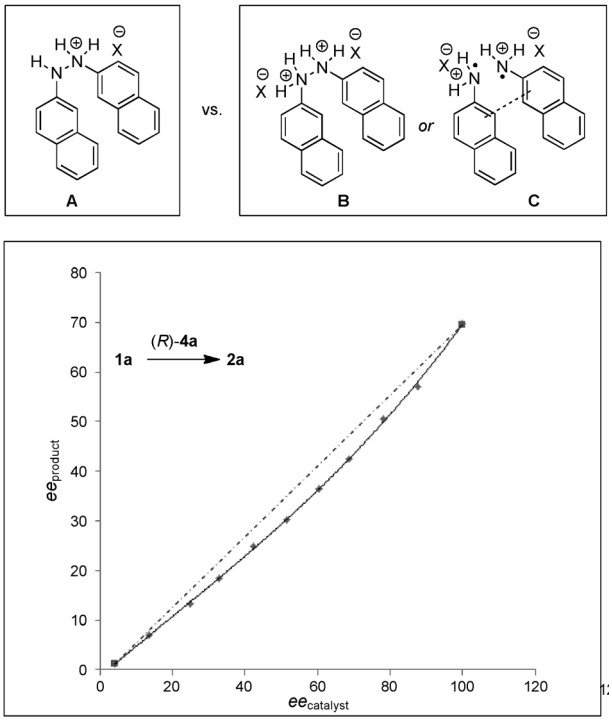
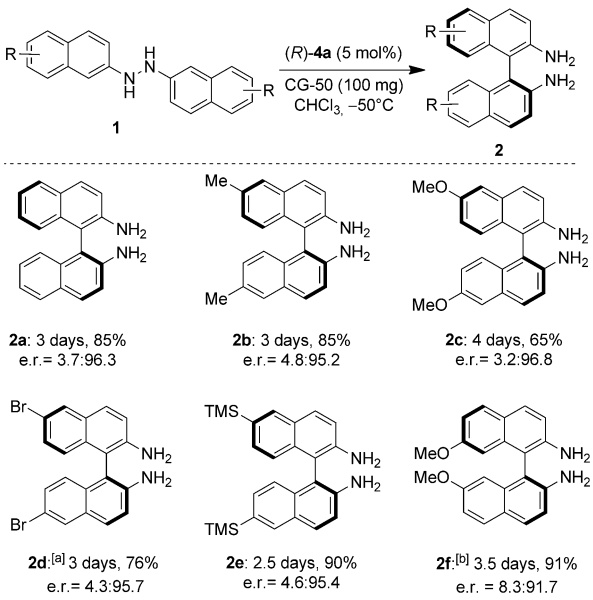


Figure 1. Observed nonlinear effects in the asymmetric catalysis of the rearrangement of **1a** to **2a**, and potential ion pair intermediates.

which of the suggested pathways is operative.[13] If the reaction indeed would proceed via a dicationic intermediate, nonlinear effects may be anticipated, since two catalyst anions would be involved in the presumably enantioselectivity-determining rearrangement step. Remarkably, in the rearrangement of substrate **1a**, we did indeed see a significant negative nonlinear effect. While there may be various alternative explanations for this observation, including the involvement of a catalyst dimer, our results are consistent with a dicationic mechanism.

In summary, we have developed a catalytic asymmetric benzidine rearrangement using a chiral phosphoric acid catalyst. With this methodology, electronically and structurally diverse axially chiral 2,2′-binaphthyldiamine (BINAM) derivatives were synthesized with a high level of enantioselectivity.[14] Current work aims at a further expansion of the asymmetric catalysis of reactions involving a diaza Cope rearrangement and at a deeper understanding of their mechanistic details.



Scheme 2. Scope of the asymmetric benzidine rearrangement. Reactions were run on a 0.1 mmol scale and the e.r. value was determined by using HPLC. [a] Reaction was run at −30 °C with 10 mol % catalyst loading. [b] Reaction was run at −45 °C with 10 mol % catalyst loading.

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[1] For reviews on Fischer indolizations, see: a) B. Robinson, *Chem. Rev.* **1969**, *69*, 227 – 250; b) B. Robinson, *Chem. Rev.* **1963**, *63*, 373 – 401.

[2] For examples of the benzidine rearrangement on a binaphthyl system, see: a) H. J. Shine, L. Kupczyk-Subotkowska, W. Subotkowski, *J. Am. Chem. Soc.* **1985**, *107*, 6674 – 6678; b) H. J. Shine, E. Gruszecka, W. Subotkowski, M. Brownawell, J. S. Filippo, *J. Am. Chem. Soc.* **1985**, *107*, 3218 – 3223; c) H. J. Shine, F.-T. Huang, R. L. Snell, *J. Org. Chem.* **1961**, *26*, 380 – 383; d) H. J. Shine, J. C. Trisler, *J. Am. Chem. Soc.* **1960**, *82*, 4054 – 4058; e) H. J. Shine, *J. Am. Chem. Soc.* **1956**, *78*, 4807 – 4809.

[3] For examples of the benzidine rearrangement on a biphenyl system, see: a) G. Ghigo, S. Osella, A. Maranzana, G. Tonachini, *Eur. J. Org. Chem.* **2011**, 2326 – 2333; b) E. S. Rhee, H. J. Shine, *J. Org. Chem.* **1987**, *52*, 5633 – 5636; c) H. J. Shine, K. H. Park, M. L. Brownawell, J. San Filippo, *J. Am. Chem. Soc.* **1984**, *106*, 7077 – 7082; d) H. J. Shine, J. Habdas, H. Kwart, M. Brechbiel, A. G. Horgan, J. San Filippo, *J. Am. Chem. Soc.* **1983**, *105*, 2823 – 2827; e) H. J. Shine, H. Zmuda, K. H. Park, H. Kwart, A. G. Horgan, M. Brechbiel, *J. Am. Chem. Soc.* **1982**, *104*, 2501 – 2509; f) H. J. Shine, G. N. Henderson, A. Cu, P. Schmid, *J. Am. Chem. Soc.* **1977**, *99*, 3719 – 3723; g) G. A. Olah, K. Dunne, D. P. Kelly, Y. K. Mo, *J. Am. Chem. Soc.* **1972**, *94*, 7438 – 7447; h) H. J. Shine, J. P. Stanley, *J. Org. Chem.* **1967**, *32*, 905 – 910; i) D. V. Banthorpe, A. Cooper, C. K. Ingold, *Nature* **1967**, *216*, 232 – 235; j) R. B. Carlin, G. S. Wich, *J. Am. Chem. Soc.* **1958**, *80*, 4023 – 4033; k) R. B. Carlin, R. C. Odioso, *J. Am. Chem. Soc.* **1954**, *76*, 2345 – 2349; l) R. B. Carlin, R. C. Odioso, *J. Am. Chem. Soc.* **1954**, *76*, 100 – 104; m) R. B. Carlin, R. G. Nelb, R. C. Odioso, *J. Am. Chem. Soc.* **1951**, *73*, 1002 – 1007; n) M. J. S. Dewar, *Nature* **1945**, *156*, 784 – 784; o) R. Robinson, *J. Chem. Soc.* **1941**, 220 – 240; p) C. K. Ingold, H. V. Kidd, *J. Chem. Soc.* **1933**, 984 – 988.

[4] a) S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534 – 18537; b) A. Martínez, M. J. Webber, S. Müller, B. List, *Angew. Chem.* **2013**, DOI: 10.1002/ange.201301618; *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201301618.

[5] For selected examples of BINAM-based oraganocatalysts, see: a) B. Tan, N. R. Candeias, C. F. Barbas, *Nat. Chem.* **2011**, *3*, 473 – 477; b) D. Uraguchi, D. Nakashima, T. Ooi, *J. Am. Chem. Soc.* **2009**, *131*, 7242 – 7243; c) S. Harada, N. Toudou, S. Hiraoka, A. Nishida, *Tetrahedron Lett.* **2009**, *50*, 5652 – 5655; d) M. Hatano, T. Ikeno, T. Matsumura, S. Torii, K. Ishihara, *Adv. Synth. Catal.* **2008**, *350*, 1776 – 1780; e) G. Guillena, M. d. C. Hita, C. Nájera, S. F. Viózquez, *J. Org. Chem.* **2008**, *73*, 5933 – 5943; f) A. Sakakura, K. Suzuki, K. Ishihara, *Adv. Synth. Catal.* **2006**, *348*, 2457 – 2465.

[6] For selected examples of BINAM-based metal catalysts see: a) D. L. Usanov, H. Yamamoto, *Angew. Chem.* **2010**, *122*, 8345 – 8348; *Angew. Chem. Int. Ed.* **2010**, *49*, 8169 – 8172; b) S. K. Alamsetti, G. Sekar, *Chem. Commun.* **2010**, *46*, 7235 – 7237; c) Y. Sudo, D. Shirasaki, S. Harada, A. Nishida, *J. Am. Chem. Soc.* **2008**, *130*, 12588 – 12589; d) H. Huang, T. Okuno, K. Tsuda, M. Yoshimura, M. Kitamura, *J. Am. Chem. Soc.* **2006**, *128*, 8716 – 8717; e) Q. Xu, W.-L. Duan, Z.-Y. Lei, Z.-B. Zhu, M. Shi, *Tetrahedron* **2005**, *61*, 11225 – 11229; f) W.-L. Duan, M. Shi, G.-B. Rong, *Chem. Commun.* **2003**, 2916 – 2917; g) K. Aikawa, K. Mikami, *Angew. Chem.* **2003**, *115*, 5616 – 5619; *Angew. Chem. Int. Ed.* **2003**, *42*, 5458 – 5461; h) N. Takenaka, Y. Huang, V. H. Rawal, *Tetrahedron* **2002**, *58*, 8299 – 8305.

[7] For the resolution of BINAM, see: a) S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénedé, *Angew. Chem.* **2009**, *121*, 4675 – 4679; *Angew. Chem. Int. Ed.* **2009**, *48*, 4605 – 4609; b) K. J. Brown, M. S. Berry, J. R. Murdoch, *J. Org. Chem.* **1985**, *50*, 4345 – 4349.

[8] a) N. Montazeri, M. Tavana, S. Yousefian, F. T. Firooz, *Asian J. Chem.* **2012**, *24*, 840 – 842; b) X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang, M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 5500 – 5511; c) S.-W. Hon, C.-H. Li, J.-H. Kuo, N. B. Barhate, Y.-H. Liu, Y. Wang, C.-T. Chen, *Org. Lett.* **2001**, *3*, 869 – 872; d) M. Smrcina, M. Lorenc, V. Hanus, P. Sedmera, P. Kocovsky, *J. Org. Chem.* **1992**, *57*, 1917 – 1920.

[9] F. Sannicolò, *Tetrahedron Lett.* **1985**, *26*, 119 – 120.

[10] During the preparation of the manuscript, a similar approach was reported: G.-Q. Li, H. Gao, C. Keene, M. Devonas, D. H. Ess, L. Kürti, *J. Am. Chem. Soc.* **2013**, *135*, 7414 – 7417.

[11] For reviews on chiral Brønsted acid catalysis, see: a) M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, I. Atodiresei, *Angew. Chem.* **2011**, *123*, 6838 – 6853; *Angew. Chem. Int. Ed.* **2011**, *50*, 6706 – 6720; b) M. Terada, *Synthesis* **2010**, 1929 – 1982; c) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395 – 456; d) M. Terada, *Chem. Commun.* **2008**, 4097 – 4112; e) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; f) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999 – 1010.

[12] For reviews on asymmetric counteranion-directed catalysis (ACDC), see: a) M. Mahlau, B. List, *Angew. Chem.* **2013**, *125*, 540 – 556; *Angew. Chem. Int. Ed.* **2013**, *52*, 518 – 533; b) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603 – 614; c) M. Mahlau, B. List, *Isr. J. Chem.* **2012**, *52*, 630 – 638; d) L. Ratjen, S. Müller, B. List, *Nachr. Chem.* **2010**, *58*, 640 – 646; e) J. Lacour, D. Moraleda, *Chem. Commun.* **2009**, 7073 – 7089; f) J. Lacour, D. Linder, *Science* **2007**, *317*, 462 – 463; g) J. Lacour, V. Hebbe-Viton, *Chem. Soc. Rev.* **2003**, *32*, 373 – 382.

[13] a) T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem.* **2009**, *121*, 464 – 503; *Angew. Chem. Int. Ed.* **2009**, *48*, 456 – 494; b) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353 – 2357.

[14] To evaluate the applicability of our method, compound **2a** was prepared on a multi-mmol scale by using 5 mol% of the commercially available catalyst (*R*)-**4a**. BINAM (**2a**) was obtained in good yield and with a high enantioselectivity; see the Supporting Information for details.

