ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Asymmetric semipinacol rearrangement of 2,3-allenols with *N*-bromo-1,8-naphthalimide†

Cite this: *Chem. Commun.*, 2014, **50**, 4445

Received 28th January 2014,
Accepted 25th February 2014

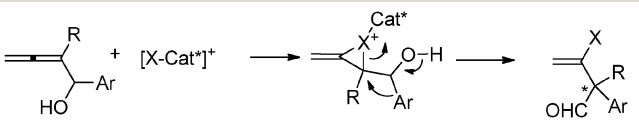
DOI: 10.1039/c4cc00767k

www.rsc.org/chemcomm

Binjie Guo, Chunling Fu* and Shengming Ma*

A method using quinidine and optically active binol-derived phosphoric acid as a cocatalyst to catalyze the asymmetric semipinacol rearrangement of 2,3-allenols forming optically active 3-bromo-3-enals that contain an all-carbon quaternary stereocenter has been developed. After some further treatments, the products with practical enantiomeric purity could be prepared.

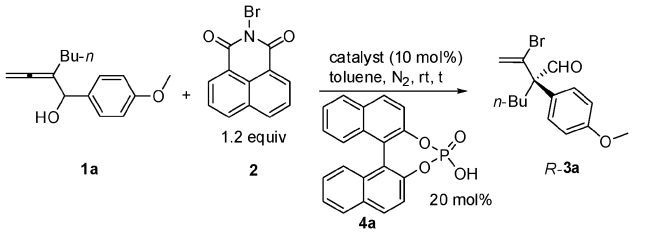
One of the most challenging topics in modern organic synthesis is asymmetric construction of chiral quaternary all-carbon stereocenters, and it has always been in high demand for the development of synthetic methodologies.[1] In our previous work,[2] we showed that 3-halo-3-enals or 2-halo-2-alkenyl ketones that contain an α-quaternary all carbon stereocenter may be formed by the electrophilic addition/1,2-shift of 2,3-allenols with X^+ (X = Br, I). We hypothesized that the semipinacol rearrangement of allenols could also be asymmetrically catalyzed to afford chiral 3-halo-3-enals that contain a quaternary all-carbon stereocenter[3,4] (Scheme 1).



Scheme 1 Asymmetric semipinacol rearrangement of 2,3-allenols.

In our initial study, 1-(4-methoxylphenyl)-2-butyl-2,3-allenol **1a** was used as a model substrate with *N*-bromo-1,8-naphthalimide **2**[5] as X^+ sources. We chose the commonly used cinchona alkaloid derivatives, such as $(DHQD)_2PYR$, $(DHQD)_2PHAL$, $(DHQD)_2PYDZ$ and $(DHQD)_2AQN$[6] as catalysts. But to our disappointment, only very low enantiomeric selectivity (<10% ee) was observed (Table 1, entries 1–4). Then, we just used the simplest quinidine as the catalyst. And to our delight, the enantioselectivity was increased to 21% ee with a yield of 79% (Table 1, entry 5). According to the literature, the use of chiral phosphoric acid as a cocatalyst may dramatically enhance the stereochemical control of cinchona alkaloid derivatives.[7] So (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (*R*-**4a**) was added as a cocatalyst. In fact, the enantiomeric excess was improved to 37% ee with a yield of 81% (Table 1, entry 6). What's more, *R*-**4a** only gave racemic **3a** in the absence of quinidine (Table 1, entry 7). Quinine in the presence of *S*-acid (*S*-**4a**) gave a yield of 92% and −30% ee (Table 1, entry 8).

Table 1 Optimization of the asymmetric reaction between allenol **1a** and **2**[a]



Entry	Catalyst	Acid	*t* (h)	Isolated yield of *R*-**3a** (%)	ee of *R*-**3a**[b] (%)
1	$(DHQD)_2PYR$	—	7	71	−8
2	$(DHQD)_2PHAL$	—	17	80	7
3	$(DHQD)_2PYDZ$	—	13.5	82	5
4	$(DHQD)_2AQN$	—	14.7	60	6
5	Quinidine (20%)	—	12	79	21
6	Quinidine (20%)	(*R*)-**4a**	2.3	81	37
7	—	(*R*)-**4a**	26	53	0
8	Quinine (20%)	(*S*)-**4a**	11	92	−30

[a] All reactions were performed with 0.1 mmol of **1a** in 2 mL of toluene unless otherwise noted. [b] Determined by HPLC analysis using a chiral stationary phase.

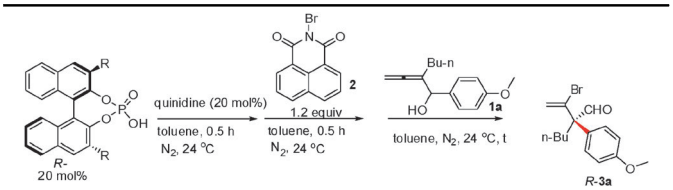
Then, other chiral-binol-derived phosphoric acids were examined. As we can see, when iodo-substituted acid (**4b**) was used, the ee value could be improved to 50% (Table 2, entry 1). A much better ee of 72% was achieved when phenyl-substituted acid (**4c**) was used (Table 2, entry 2). Further optimization on the phenyl group, such as the bulky *t*-butyl group (**4d**), the electron-donating group (4-MeO (**4e**), 4-Me (**4f**)), the electron-withdrawing group (4-CF_3, **4g**) and 4-phenyl (**4h**)

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou, 310027, Zhejiang, P. R. China.
E-mail: masm@sioc.ac.cn; Fax: +86-21-6416-7510

† Electronic supplementary information (ESI) available: CCDC 980926. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00767k

gave no better results (Table 2, entries 3–7). When the 2-naphthyl (**4i**) or the 9-anthryl (**4j**) group was introduced instead of the phenyl group, we observed 53% ee and 30% ee, respectively (Table 2, entries 8 and 9). When the styryl (**4k**) group was introduced, the ee value dropped to 48% with a yield of 75% (Table 2, entry 10). Alcohols have been used as additives in some reports,[3g] due to the possible formation of the hydrogen bond enhancing the stereoselectivity of the catalyst. To our delight, we found that the addition of 10 mol% of MeOH could slightly improve the ee value to 74% and gave a yield of 82% even with 15 mol% of quinidine and 5 mol% of *R*-phenyl-acid (**4c**) (Table 1, entry 11). Other conditions such as solvent effect, temperature, the ratio of catalysts, additives and X^+ sources have also been screened (see ESI†), but no better results were achieved.

Table 2 Optimization of the asymmetric semipinacol rearrangement of allenol **1a**[a]

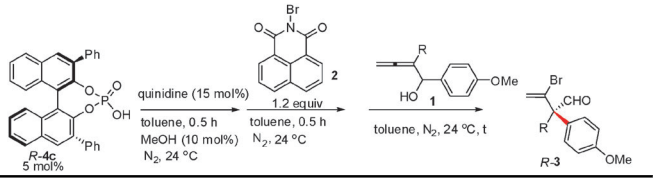


Entry	R	*t* (h)	Yield of *R*-**3a**[b] (%)	ee of *R*-**3a**[c] (%)
1	I (**4b**)	11.5	81	50
2	Ph (**4c**)	12.3	80	72
3	4-*t*-BuC_6H_4 (**4d**)	3.8	85	59
4	4-MeOC_6H_4 (**4e**)	3.7	88	33
5	4-MeC_6H_4 (**4f**)	4.8	76	59
6	4-$CF_3C_6H_4$ (**4g**)	16	75	60
7	4-PhC_6H_4 (**4h**)	13	89	43
8	2-Naphthyl (**4i**)	3.7	88	53
9	9-Anthryl (**4j**)	4.3	81	30
10	Styryl (**4k**)	11	75	48
11[d]	Ph (**4c**)	3	82	74
12[d,e]	Ph (**4c**)	2.7	73	27
13[d,f]	Ph (**4c**)	1	68	8
14[d,g]	Ph (**4c**)	25	~75	53

[a] All reactions were performed with 0.1 mmol of **1a** in 2 mL of toluene unless otherwise noted. [b] Yield of an isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 15 mol% of quinidine, 5 mol% of **4c** and 10 mol% of MeOH were used. [e] NBS was used instead of **2**. [f] 1,3-Dibromohydantoin was used instead of **2**. [g] The reaction was conducted at −30 °C.

With the optimized reaction conditions in hand, we studied the scope of this reaction with the typical results summarized in Table 3. Allenols with alkyl groups on the 2-position mostly gave an ee value over 70%. For example, when the ethyl group (**1b**) was introduced, **3b** was produced with a yield of 77% and 77% ee (Table 3, entry 2). Propyl (**1c**), pentyl (**1d**), hexyl (**1e**) and decyl (**1f**) substituted allenols gave 83–87% yields and 72–77% ee (Table 3, entries 3–6). For secondary alkyl groups, probably due to the steric effect, iso-propyl (**1g**) and cyclohexyl (**1h**) substituted allenols gave the products with lower ee values of 66% and 64%, respectively (Table 3, entries 7 and 8). To our delight, when the allyl group (**1i**) was introduced, **3i** was afforded with a yield of 78% and 76% ee: no reaction occurred to the allylic C=C bond (Table 3, entry 9). When the benzyl group (**1j**) was introduced, **3j** was afforded with a yield of 75% and 78% ee (Table 3, entry 10), while 2-(3-phenylpropyl) substituted enal (**3k**) was afforded with a yield of 80% and 71% ee (Table 3, entry 11). Interestingly, it was observed that with the parent phenyl (**1l**) group, the result was rather poor with only 8% ee of **3l** (Table 3, entry 12).

Table 3 The scope of the asymmetric semipinacol rearrangement of allenol[a]

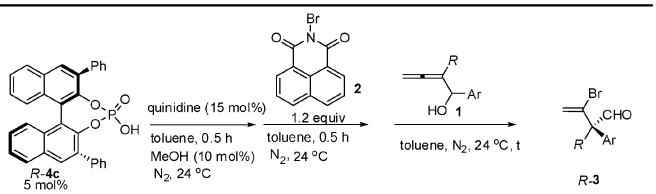


Entry	R	*t* (h)	Yield of *R*-**3**[b] (%)	ee of *R*-**3**[c] (%)
1	*n*-Bu (**1a**)	3.2	75 (**3a**)	75
2	Et (**1b**)	2.5	77 (**3b**)	77
3	*n*-C_3H_7 (**1c**)	3	83 (**3c**)	77
4	*n*-C_5H_{11} (**1d**)	4.2	87 (**3d**)	73
5	*n*-C_6H_{13} (**1e**)	2.5	85 (**3e**)	72
6	*n*-$C_{10}H_{21}$ (**1f**)	4	83 (**3f**)	73
7	i-Pr (**1g**)	3	70 (**3g**)	66
8	*c*-C_6H_{11} (**1h**)	3	98 (**3h**)	64
9	Allyl (**1i**)	3	78 (**3i**)	76
10	Bn (**1j**)	11.5	75 (**3j**)	78
11	Ph$(CH_2)_3$ (**1k**)	3	80 (**3k**)	71
12[d]	Ph (**1l**)	3	59 (**3l**)	8

[a] All reactions were performed with 0.5 mmol of **1** in 10 mL of toluene unless otherwise noted. [b] Yield of an isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The reaction was conducted on a 0.2 mmol scale of **1l**.

It is interesting to observe that the electronic nature of the aryl group may also influence the enantioselectivity of the reaction: 1-(4-ethoxyl)phenyl substituted allenol (**1m**) gave almost the same results: 80% yield and 73% ee (Table 4, entry 1); allenol **1n** with the 3,4-methylenedioxyphenyl group on the 1-position gave a yield of 65% and a little lower 62% ee (Table 4, entry 2); it is worth noting that a heteroaryl such as 2-thienyl substituted allenol **1o** may also afford the product in 73% yield and 68% ee under the standard reaction conditions (Table 4, entry 3). However, when the aryl group was replaced with the 4-MeC_6H_4 (**1q**) group, both the yield and ee of the products dropped (Table 4, entry 5).

Table 4 The scope of the asymmetric semipinacol rearrangement of allenol[a]



Entry	Ar	R	*t* (h)	Yield of *R*-**3**[b] (%)	ee of *R*-**3**[c] (%)
1	4-EtOC_6H_4 (**1m**)	*n*-Bu	3.3	80 (**3m**)	73
2	3,4-$OCH_2OC_6H_3$ (**1n**)	*n*-Bu	3.3	65 (**3n**)	62
3	2-Thienyl (**1o**)	*n*-Bu	3	73 (**3o**)[d]	68
4	3,4,5-$(MeO)_3C_6H_2$ (**1p**)	Et	16.7	61 (**3p**)	61
5	4-MeC_6H_4 (**1q**)	*n*-Bu	5.5	54 (**3q**)	54

[a] All reactions were performed with 0.5 mmol of **1** in 10 mL of toluene unless otherwise noted. [b] Yield of an isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The absolute configuration of **3o** is *S* according to the sequence rule.

It is worth noting that after recrystallization[8] from the solution of CH_2Cl_2 and *n*-hexane three times, the ee value of **3k** reached 99% (17% yield). The absolute configuration of **3k** was determined by the X-ray diffraction study[9] (Fig. 1). A large scale reaction of **1k** (882.5 mg, 3.0 mmol) was also conducted and the ee value of **3k** reached 94% after twice recrystallization with 40% yield (for details, see the ESI†).

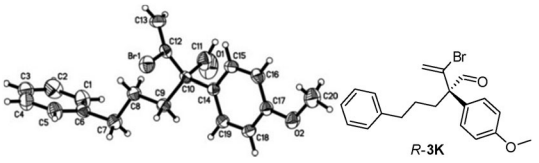
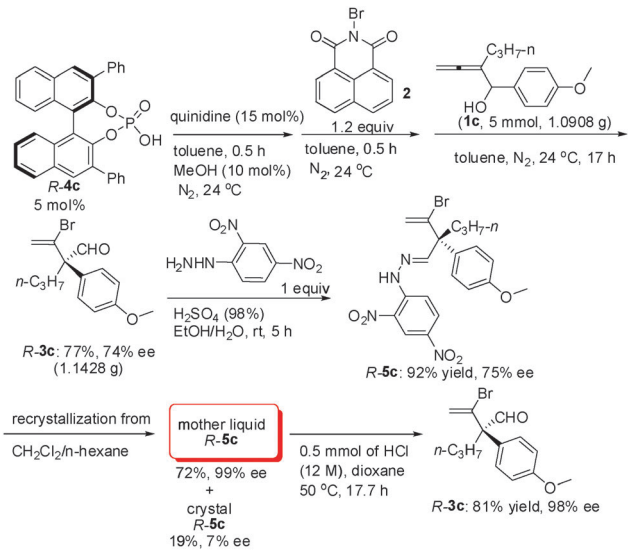


Fig. 1 X-ray diffraction study of *R*-**3k**.

To demonstrate the practicality of this reaction, another gram-scale reaction of **1c** was further conducted. The reaction of **1c** (1.0908 g, 5.0 mmol) with **2** afforded the corresponding product **3c** (1.1428 g) with a yield of 77% and 74% ee. Further treatment of **3c** with 2,4-dinitrophenylhydrazine in the mixed solution of EtOH and H_2O catalyzed by H_2SO_4 (98%) gave hydrazone **5c** in a yield of 92% and 75% ee. After crystallization from the solution of CH_2Cl_2 and *n*-hexane, the crystals (7% ee, 19% yield) were removed and evaporation of the mother liquid gave the optically active enantiomer with 99% ee (72% yield), which was then dried, and subsequently stirred in the solution of dioxane with concentrated hydrochloric acid (12 M) at 50 °C for 17.7 h to afford enal *R*-**3c** in a yield of 81% and 98% ee (Scheme 2).



Scheme 2 Preparation of *R*-**3c** with 98% ee.

In conclusion, we have developed a method using quinidine and chiral-binol-derived phosphoric acid as a cocatalyst to catalyze the asymmetric semipinacol rearrangement of 2,3-allenols forming chiral 3-bromo-3-enals that contain a quaternary all-carbon stereocenter. With further treatments, the 3-bromo-3-enals with practical enantiomeric excess may be prepared. However, the real identity of the catalyst has not been established. Due to the easy availability of the allenols, the catalysts, and the potential of the highly functionalized aldehydes, this method will be of high interest to the community. Further study on this reaction is being actively pursued in this laboratory.

Financial support from the National Basic Research Program of China (2011CB808700) and the National Nature Science Foundation of China (21232006) is greatly appreciated. Shengming Ma is a Qiu Shi Adjunct Professor at the Zhejiang University. We thank Miss Qiong Yu in this group for reproducing the results presented in Table 3, entries 2 and 9, and entry 2 in Table 4.

Notes and references

1 *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, ed. J. Christoffers and A. Baro, Wiley-VCH, Weinheim, Germany, 2005. For recent reviews on the asymmetric formation of quaternary carbon centers, see: (*a*) C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363; (*b*) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369; (*c*) P. G. Cozzi, R. Hilgraf and N. Zimmermann, *Eur. J. Org. Chem.*, 2007, 5969; (*d*) M. Bella and T. Gasperi, *Synthesis*, 2009, 1583.

2 (*a*) C. L. Fu, J. Li and S. M. Ma, *Chem. Commun.*, 2005, 4119–4121; (*b*) J. Li, C. L. Fu, G. Chen, G. Chai and S. M. Ma, *Adv. Synth. Catal.*, 2008, **350**, 1376–1382.

3 For recent articles on the formation of quaternary carbon stereocenters *via* semipinacol rearrangement see: (*a*) B. M. Trost and T. Yasukata, *J. Am. Chem. Soc.*, 2001, **123**, 7162; (*b*) B. M. Wang, L. Song, C. A. Fan, Y. Q. Tu and W. M. Chen, *Synlett*, 2003, 1497–1499; (*c*) M. Wang, B. M. Wang, L. Shi, Y. Q. Tu, C. A. Fan, S. H. Wang, X. D. Hu and S. Y. Zhang, *Chem. Commun.*, 2005, 5580–5582; (*d*) F. Kleinbeck and F. D Toste, *J. Am. Chem. Soc.*, 2009, **131**, 9178; (*e*) E. Zhang, C. A. Fan, Y. Q. Tu, F. M. Zhang and Y. L Song, *J. Am. Chem. Soc.*, 2009, **131**, 14626; (*f*) Q. W. Zhang, C. A. Fan, H. J. Zhang, Y. Q. Tu, Y. M. Zhao, P. M. Gu and Z. M. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 8572; (*g*) Z. M. Chen, Q. W. Zhang, Z. H. Chen, H. Li, Y. Q. Tu, F. M. Zhang and J. M. Tian, *J. Am. Chem. Soc.*, 2011, **133**, 8818–8821; (*h*) H. Li, F. M. Zhang, Y. Q. Tu, Q. W. Zhang, Z. M. Chen, Z. H. Chen and J. Li, *Chem. Sci.*, 2011, **2**, 1839–1841; (*i*) C. H. Muller, M. Wilking, A. Ruhlmann, B. Wibbeling and U. Henneche, *Synlett*, 2011, 2043; (*j*) Z. M. Chen, B. M. Yang, Z. H. Chen, Q. W. Zhang, M. Wang and Y. Q. Tu, *Chem.–Eur. J.*, 2012, **18**, 12950–12954.

4 (*a*) F. Romanov-Michailidis, L. Guenee and A. Alexakis, *Angew. Chem., Int. Ed.*, 2013, **52**, 9266–9270; (*b*) F. Romanov-Michailidis, L. Guenee and A. Alexakis, *Org. Lett.*, 2013, **15**, 5890; (*c*) B. Alcaide, P. Almendros, A. Luna, S. Cembellin, M. Arno and L. R. Domingo, *Chem.–Eur. J.*, 2011, **17**, 11559; (*d*) B. Alcaide, P. Almendros, A. Luna and M. R. Torres, *Adv. Synth. Catal.*, 2010, **352**, 621.

5 Compound **2** was synthesized according to the literature: S. Fujisaki, S. Hamura, H. Eguchi and A. Nishida, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2426–2428.

6 (*a*) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Q. Xu and X. L. Zhang, *J. Org. Chem.*, 1992, 2768–2771; (*b*) G. A. Crispino, K. S. Jeong, H. C. Kolb, Z. M. Wang, D. Q. Xu and K. B. Sharpless, *J. Org. Chem.*, 1993, 3785–3786.

7 (*a*) J. W. Xie, X. Huang, L. P. Fan, D. C. Xu, X. S. Li, H. Su and Y. H. Wen, *Adv. Synth. Catal.*, 2009, **351**, 3077–3082; (*b*) G. Bergonzini, S. Vera and P. Melchiorre, *Angew. Chem.*, 2010, **122**, 9879–9882 (*Angew. Chem., Int. Ed.*, 2010, **49**, 9685–9688); (*c*) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo and P. Melchiorre, *J. Am. Chem. Soc.*, 2011, **133**, 17934–17941; (*d*) O. Lifchits, M. Reisinger and B. List, *J. Am. Chem. Soc.*, 2010, **132**, 10227–10229; (*e*) J. Song, C. Guo, A. Adele, H. Yin and L. Gong, *Chem.–Eur. J.*, 2013, **19**, 3319–3323.

8 W. L. F. Armarego and C. L. L. Chai, *Purification of Laboratory Chemicals*, Elsevier Inc., 5th edn, 2003, pp. 14–17ISBN: 978-0-7506-7571-0.

9 Crystal data for compound **3k**: $C_{20}H_{21}BrO_2$, M_W = 373.28, Monoclinic, space group *P*21, final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0472, wR_2 = 0.0921, *R* indices (all data) R_1 = 0.0723, wR_2 = 0.1047, *a* = 10.7903 (11) Å, *b* = 8.3733 (5) Å, *c* = 10.8570 (9) Å, α = 90°, β = 110.884 (10)°, γ = 90°, *V* = 916.49(13) Å^3, *T* = 293 (2) K, *Z* = 2, reflections collected/unique: 6043/2460 (R_{int} = 0.0344), number of observations [$>2\sigma(I)$] 3325, parameters: 209. CCDC 980926.