D-Camphor-derived triazolium salts for catalytic intramolecular crossed aldehyde–ketone benzoin reactions†

Yi Li, Zhen Feng and Shu-Li You*

Received (in Cambridge, UK) 18th January 2008, Accepted 19th February 2008
First published as an Advance Article on the web 13th March 2008
DOI: 10.1039/b801004h

A series of triazolium salts has been synthesized from D-camphor and found to be efficient catalysts for intramolecular crossed aldehyde–ketone benzoin reactions, affording α-ketols bearing a quaternary carbon center with up to 93% ee.

N-Heterocyclic carbene (NHC) catalyzed intramolecular crossed aldehyde–ketone benzoin reactions[1] have been recently successfully developed by Suzuki and Enders, respectively. This reaction evoked enormous synthetic interests because of the unique reaction model and significant importance of the products. For example, Suzuki and co-workers have shown the successful application of this reaction in the elegant total synthesis of functionalized preanthraquinones and (+)-sappanone B.[1a,2] More recently, the asymmetric version of this intramolecular crossed aldehyde–ketone benzoin reaction has been realized by the same two groups,[2e,3] generating a quaternary alcohol stereocenter with high ees in many cases. However, the successful catalysts for this reaction remain limited. In addition, the yields of the crossed benzoin products are only low to moderate in some cases mainly due to the aldol side reaction. Therefore, design and synthesis of novel *N*-heterocyclic carbene catalysts, especially from those readily available chiral sources, remain the focus of the study in catalytic intramolecular crossed aldehyde–ketone benzoin reactions, even for the NHC-catalyzed organic reactions in general.[4,5] On the other hand, camphor exists extensively in nature and has been widely used as the source for chiral auxiliaries and chiral ligands in asymmetric synthesis.[6] The fact that both of the enantiomers of camphor are commercially available guarantees the access to either enantiomer of the chiral products. We therefore envisaged that camphor might be an efficient chiral scaffold for *N*-heterocyclic carbene catalysts. As our continuing endeavors to develop new *N*-heterocyclic carbenes and their applications in novel organocatalytic reactions,[7] in this communication, we report our preliminary results on the synthesis of novel chiral triazolium salts from D-camphor and their applications in asymmetric catalytic intramolecular crossed aldehyde–ketone benzoin reactions.

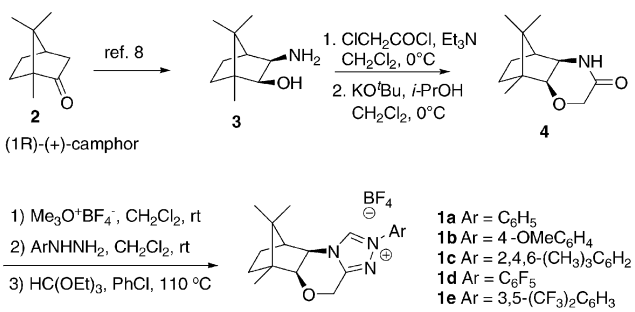
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China. E-mail: slyou@mail.sioc.ac.cn; Fax: (+86) 21-54925087

† Electronic supplementary information (ESI) available: Experimental procedures and analysis data for new compounds. CCDC 671038 (for **1c**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b801004h

Triazolium salts **1** were synthesized from D-camphor as outlined in Scheme 1. The synthesis commences from the transformation of D-camphor to the *exo*-amino alcohol **3** according to the reported method.[8] Cyclization of **3** using the modified one-pot procedure employing chloroacetyl chloride afforded the lactam **4** in an overall 66% yield.[9] Several homologous triazolium salts **1a–e** were then generated in analogy to the literature experiments developed by Rovis and co-workers.[10] These triazolium salts could be separated by column chromatography and further purified by recrystallization in hexane/ethyl acetate. In addition, the relative stereochemistry of **1c** was confirmed by an X-ray crystallographic analysis as shown in Fig. 1 (see ESI†). The absolute stereochemistry could be deduced from the known D-camphor stereochemistry.

Intramolecular crossed benzoin reaction of aldehyde–ketone **5a** was chosen as the model reaction to test the catalytic activity of the new triazolium salts since the resultant crossed benzoin products are 4-chromanone derivatives, widely existing in many bioactive natural products.[2,11] As summarized in Table 1, when triazolium salts **1a–c** (12 mol%) were used together with Et_3N (10 mol%), only trace amount of desired α-ketol **6a** was observed together with byproducts such as **7a and 8a** (entries 1–3, Table 1). To our delight, under the same conditions, triazolium salt **1d** showed excellent reactivity and quite promising asymmetric induction (95% yield, 71% ee, entry 4, Table 1). It is worthy of note that there is no aldol byproduct **7a** or benzofuran **8a** which was obtained in 27% combined yield when Suzuki's modified precatalyst was used for the same substrate.[3d] When triazolium salt **1e** was used, α-ketol **6a** was obtained in 60% yield with 18% ee, together with a significant amount of aldol byproduct.

Utilizing the salt **1d** as the precatalyst, various solvents such as CH_2Cl_2, Et_2O, ^{t}BuOH, DMF, and THF were tested and found to be well tolerated in this reaction (entries 6–10,



Scheme 1 Synthesis of triazolium salts **1** from D-camphor.

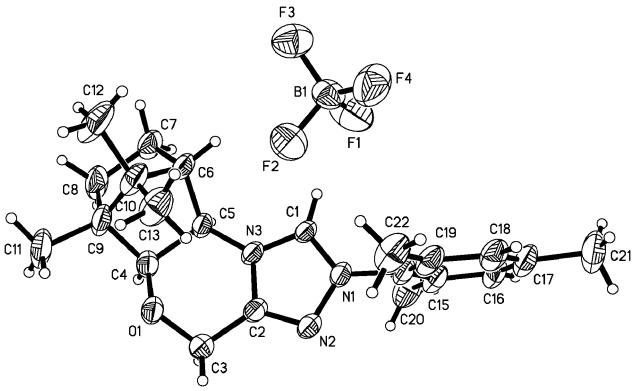
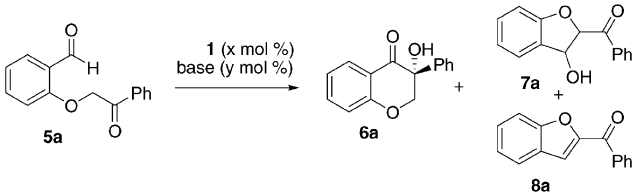


Fig. 1 X-Ray crystal structure of triazolium salt **1c**. Thermal ellipsoids are set at 30% probability.

Table 1). Reaction in THF led to an optimal combination of 96% yield and 84% ee. Lowering the catalyst loading from 10 to 5 mol% also gave an excellent yield of the desired cyclization product but with a small erosion of the ee value, however, further decreasing the catalyst loading to 1 mol% resulted a significant drop in yield but a good ee was retained (entries 11 and 12, Table 1). With 5 mol% of the catalyst in THF, several conventional bases including inorganic bases such as KO^{t}Bu were found tolerable and DBU was optimal in terms of both yield and ee of the product (entries 13–17, Table 1).

Under these optimized conditions (that is, with 5 mol% prior generated carbene at a substrate concentration of 0.1 M

Table 1 Screening NHC catalysts and optimizing conditions for intramolecular crossed aldehyde–ketone benzoin reaction of **5a**[a]



Entry	**1** (x)	Base (y)	Solvent	Yield[b] (%)	ee[c] (%)
1	**1a** (12)	Et_3N (10)	Toluene	<5	ND
2	**1b** (12)	Et_3N (10)	Toluene	<5	ND
3	**1c** (12)	Et_3N (10)	Toluene	<5	ND
4	**1d** (12)	Et_3N (10)	Toluene	95	71
5	**1e** (12)	Et_3N (10)	Toluene	60	18
6	**1d** (12)	Et_3N (10)	CH_2Cl_2	91	78
7	**1d** (12)	Et_3N (10)	Et_2O	94	73
8	**1d** (12)	Et_3N (10)	^{t}BuOH	75	81
9	**1d** (12)	Et_3N (10)	DMF	60	85
10	**1d** (12)	Et_3N (10)	THF	96	84
11	**1d** (6)	Et_3N (5)	THF	98	79
12	**1d** (1.2)	Et_3N (1)	THF	52	81
13	**1d** (6)	DIEA (5)	THF	93	83
14	**1d** (6)	Pyridine (5)	THF	50	85
15	**1d** (6)	KO^{t}Bu (5)	THF	92	79
16	**1d** (6)	PS (5)	THF	95	82
17	**1d** (6)	DBU (5)	THF	93	84

[a] *Reaction conditions*: 0.1 M solution, addition of **5a** to the prior generated catalyst. [b] Isolated yields. [c] Determined by chiral HPLC (Chiracel Daicel AD-H).

Table 2 Enantioselective intramolecular crossed aldehyde–ketone benzoin reaction using **1d**[a]

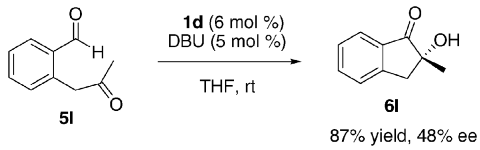
Entry	Substrate (R^1, R^2)	Product	t/h	Yield[b] (%)	ee[c] (%)
1	**5a** (H, Ph)	**6a**	6	93	84
2	**5b** (3-MeO, Ph)	**6b**	5	96	76
3	**5c** (4-MeO, Ph)	**6c**	3	99	87
4	**5d** (4-Me, Ph)	**6d**	3	92	78
5	**5e** (5-NO_2, Ph)	**6e**	2	95	93
6	**5f** (5-Cl, Ph)	**6f**	1	94 (95)[d]	90 (85)[d]
7	**5g** (3-MeO, 4-ClC_6H_5)	**6g**	3	96	76
8	**5h** (H, 4-$MeOC_6H_5$)	**6h**	3	93	90
9	**5i** (H, 4-MeO-3-BrC_6H_4)	**6i**	1.5	99	87
10	**5j** (H, Me)	**6j**	2	94	2
11	**5k** (H, ^{t}Bu)	**6k**	36	<5	—

[a] *Reaction conditions*: 0.1 M solution in THF, **5** : **1d** : DBU 1 : 0.06 : 0.05, addition of **5** to the prior generated catalyst. [b] Isolated yields. [c] Determined by chiral HPLC. [d] The number in the parenthesis indicates the result for the reaction at −10 °C.

in THF at room temperature), various aldehyde–ketone substrates were tested and the results are summarized in Table 2. Substrates **5b–f** bearing either electron-donating groups (MeO, Me, entries 2–4, Table 2) or electron-drawing groups (NO_2, Cl, entries 5 and 6, Table 2) on the salicylaldehyde-structure were well tolerated and led to their corresponding crossed benzoin products in excellent yields (92–99%) and generally high ees (76–93%). For substrate **5f**, the reaction proceeded to completion smoothly at −10 °C, affording the desired product **6f** in an excellent yield (95%) but with a slightly lower ee value (85%). The enantiomeric excess stays at the same level when the substituent on the aryl ketone moiety is either an electron-donating group or electron-withdrawing group (entries 7 and 8, Table 2). Cyclization of disubstituted aryl ketone **5i** occurred also efficiently to give ketol **6i** in a nearly quantitative yield with 87% ee (entry 9, Table 2). Unfortunately, when methyl ketone **5j** was used, cyclization product **6j** was afforded with only 2% ee although the yield remained excellent (entry 11, Table 2). No reaction occurred for *tert*-butyl ketone **5k**, probably due to the steric bulkiness of the *tert*-butyl group (entry 12, Table 2).

In addition to the O-tethered substrates **5a–k** that afforded 4-chromanone derivatives, substrate **5l** was also examined and led to an all-carbon five-membered ring having a tertiary alcohol stereocenter (Scheme 2). As shown in Scheme 2, under these optimal reaction conditions, the desired crossed benzoin product **6l** was obtained in an excellent yield of 87% with a moderate enantioselectivity of 48% ee.

In summary, we have synthesized a series of novel triazolium salts from readily available D-camphor. The NHC catalyst derived from **1d** and DBU is found to be efficient for intramolecular crossed aldehyde–ketone benzoin reaction, and α-ketols containing a quaternary stereogenic center are formed in excellent yields with up to 93% ee. Further application of



Scheme 2 Enantioselective intramolecular crossed aldehyde–ketone benzoin reaction of **5l**.

the methodology in organic synthesis and development of new enantioselective catalytic reactions by these camphor-derived triazolium salts are currently underway.

We gratefully acknowledge the Knowledge Innovation Program of the Chinese Academy of Sciences, the National Natural Science Foundation of China, and the Science and Technology Commission of Shanghai Municipality (07pj14106, 07JC14063) for generous financial support.

Notes and references

1 (*a*) Y. Hachisu, J. W. Bode and K. Suzuki, *J. Am. Chem. Soc.*, 2003, **125**, 8432; (*b*) Y. Hachisu, J. W. Bode and K. Suzuki, *Adv. Synth. Catal.*, 2004, **346**, 1097; (*c*) D. Enders and O. Niemeier, *Synlett*, 2004, 2111. For an intramolecular crossed aldehyde-aldehyde benzoin reaction; (*d*) S. M. Mennen and S. J. Miller, *J. Org. Chem.*, 2007, **72**, 5260.

2 (*a*) T. Saitoh, S. Sakashita, H. Nakata, T. Shimokawa, J. Kinjo, J. Yamahara, M. Yamasaki and T. Nohara, *Chem. Pharm. Bull.*, 1986, **34**, 2506; (*b*) M. Namikoshi, H. Nakata, H. Yamada, M. Nagai and T. Saitoh, *Chem. Pharm. Bull.*, 1987, **35**, 2761; (*c*) M. Namikoshi and T. Saitoh, *Chem. Pharm. Bull.*, 1987, **35**, 3597; (*d*) M. T. T. Nguyen, S. Awale, Y. Tezuka, Q. Le Tran and S. Kadota, *Chem. Pharm. Bull.*, 2005, **53**, 984; (*e*) H. Takikawa and K. Suzuki, *Org. Lett.*, 2007, **9**, 2713.

3 (*a*) D. Enders, O. Niemeier and T. Balensiefer, *Angew. Chem., Int. Ed.*, 2006, **45**, 1463; (*b*) H. Takikawa, Y. Hachisu, J. W. Bode and K. Suzuki, *Angew. Chem., Int. Ed.*, 2006, **45**, 3492; (*c*) D. Enders, O. Niemeier and G. Raabe, *Synlett*, 2006, 2431.

4 For reviews on NHC as organocatalysts: (*a*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534; (*b*) J. S. Johnson, *Angew. Chem., Int. Ed.*, 2004, **43**, 1326; (*c*) M. Christmann, *Angew. Chem., Int. Ed.*, 2005, **44**, 2632; (*d*) K. Zeitler, *Angew. Chem., Int. Ed.*, 2005, **44**, 7506; (*e*) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988; (*f*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606.

5 For recent examples on NHC as organocatalysts: (*a*) J. J. Song, Z. Tan, J. T. Reeves, N. K. Yee and C. H. Senanayake, *Org. Lett.*, 2007, **9**, 1013; (*b*) D. A. Culkin, W. Jeong, S. Csihony, E. D. Gomez, N. P. Balsara, J. L. Hedrick and R. M. Waymouth, *Angew. Chem., Int. Ed.*, 2007, **46**, 2627; (*c*) E. M. Phillips, M. Wadamoto, A. Chan and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 3107; (*d*) O. Coulembier, M. K. Kiesewetter, A. Mason, P. Dubois, J. L. Hedrick and R. M. Waymouth, *Angew. Chem., Int. Ed.*, 2007, **46**, 4719; (*e*) P.-C. Chiang, J. Kaeobamrung and J. W. Bode, *J. Am. Chem. Soc.*, 2007, **129**, 3520; (*f*) A. Chan and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 5335; (*g*) W. Jeong, J. L. Hedrick and R. Waymouth, *J. Am. Chem. Soc.*, 2007, **129**, 8414; (*h*) M. Wadamoto, E. M. Phillips, T. E. Reynolds and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 10098; (*i*) L. He, T.-Y. Jian and S. Ye, *J. Org. Chem.*, 2007, **72**, 7466; (*j*) H. U. Vora and T. Rovis, *J. Am. Chem. Soc.*, 2007, **129**, 13796; (*k*) J. W. Bode and S. S. Sohn, *J. Am. Chem. Soc.*, 2007, **129**, 13798; (*l*) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao and S. Ye, *Org. Lett.*, 2008, **2**, 277.

6 Selected examples: (*a*) S. Ye, Z.-Z. Huang, C.-A. Xia, Y. Tang and L.-X. Dai, *J. Am. Chem. Soc.*, 2002, **124**, 2432; (*b*) M. Kitamura, H. Oka, S. Suga and R. Noyori, *Org. Synth.*, 2003, **79**, 139; (*c*) H. Y. Kim, A. E. Lurain, P. García-García, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.*, 2005, **127**, 13138; (*d*) R. J. Kloetzing, T. Thaler and P. Knochel, *Org. Lett.*, 2006, **8**, 1125; (*e*) X.-M. Deng, P. Cai, S. Ye, X.-L. Sun, W.-W. Liao, K. Li, Y. Tang, Y.-D. Wu and L.-X. Dai, *J. Am. Chem. Soc.*, 2006, **128**, 9730.

7 (*a*) G.-Q. Li, L.-X. Dai and S.-L. You, *Chem. Commun.*, 2007, 852; (*b*) G.-Q. Li, Y. Li, L.-X. Dai and S.-L. You, *Org. Lett.*, 2007, **9**, 3519.

8 Y.-K. Chen, S.-J. Jeon, P. J. Walsh, W. A. Nugent, C. Kendall and P. Wipf, *Org. Synth.*, 2005, **82**, 87.

9 K. S. Liu and Y. S. Ding, *Chirality*, 2004, **16**, 475.

10 M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Org. Chem.*, 2005, **70**, 5725.

11 (*a*) M. G. Quaglia, N. Desideri, E. Bossu, R. Sgro and C. Conti, *Chirality*, 1999, **11**, 495; (*b*) Y. Noda and M. Watanabe, *Helv. Chim. Acta*, 2002, **85**, 3473; (*c*) H. Y. Chen, K. D. Dykstra, E. T. Birzin, K. Frisch, W. Chan, Y. T. Yang, R. T. Mosley, F. DiNinno, S. P. Rohrer, J. M. Schaeffer and M. L. Hammond, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1417.