ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 5781–5783

www.rsc.org/chemcomm

COMMUNICATION

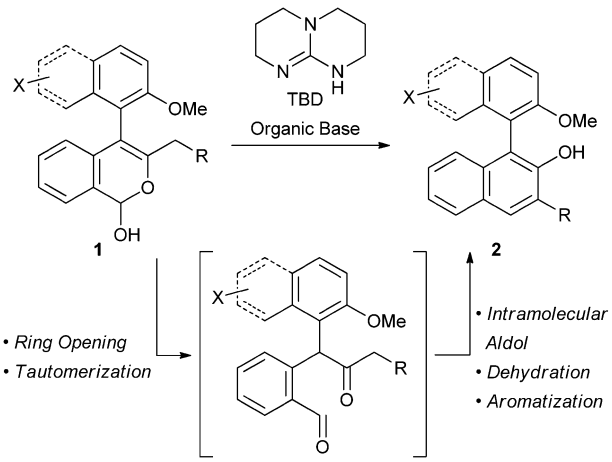
Synthesis of unsymmetrically substituted 2,2′-dihydroxy-1,1′-biaryl derivatives using organic-base-catalyzed Ferrier-type rearrangement as the key step†

Masahiro Terada*[ab] and Katsunori Dan[a]

Received 2nd March 2012, Accepted 16th April 2012
DOI: 10.1039/c2cc31594g

A strong organic base, TBD, functioned as a unique catalyst for the intramolecular multi-step transformation of lactols using the Ferrier-type rearrangement as the key step to provide unsymmetrically substituted 2,2′-dihydroxy biaryl compounds having four *ortho* substituents about the biaryl axis without the need for a metal catalyst.

Axially chiral 2,2′-dihydroxy-1,1′-biaryl skeletons are widely utilized as versatile chiral sources for ligands and auxiliaries in asymmetric synthesis.[1,2] Notably, C_2-symmetric binaphthol derivatives, which are a very important class of structural motifs, have been extensively applied to the design of enantioselective catalysts and a number of methodologies have been established to introduce substituents at the 3,3′- and other positions of the binaphthyl frameworks. Unsymmetrically substituted C_1-symmetric biaryl compounds have received much attention in recent years. Indeed, the tremendous progress in the development of enantioselective catalysts using C_1-symmetric biaryls has underscored their potential as efficient chiral ligands.[2] However, in most cases, these unsymmetrically substituted biaryl compounds have been prepared through the desymmetrization of symmetrical biaryl compounds by the introduction of a substituent to one of two reaction sites. Although a few examples of oxidative cross-coupling reactions with two different 2-naphthols[3] and transition-metal-catalyzed cross-coupling reactions to give unsymmetrical biaryls have been brilliantly demonstrated,[4] their substrate scopes have had limited success because of the strong dependence on the redox potential of the reactants and the limitation on the introduction of substituents at the three *ortho* positions about the biaryl axis, respectively. In order to develop a novel method for the synthesis of unsymmetrically substituted 2,2′-dihydroxy-1,1′-biaryl derivatives, we envisioned an unprecedented intramolecular multi-step transformation of lactols **1** catalyzed by an organic base using the Ferrier-type rearrangement as the key step (Scheme 1).[5] Herein we report that the strong organic base, TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene), functioned as an efficient catalyst for the proposed multi-step transformation that involved (i) ring opening of lactol **1** catalyzed by TBD to generate an intermediate keto aldehyde through keto–enol tautomerization; (ii) subsequent intramolecular aldol reaction [from (i) to (ii): Ferrier-type rearrangement] to afford a hydroxyl ketone; (iii) dehydration of the aldol product; and (iv) termination by aromatization, giving rise to biaryl products **2**. The method enabled efficient access to unsymmetrically substituted 2,2′-dihydroxy-1,1′-biaryl derivatives **2** having four *ortho* substituents about the biaryl axis without the need for a metal catalyst.



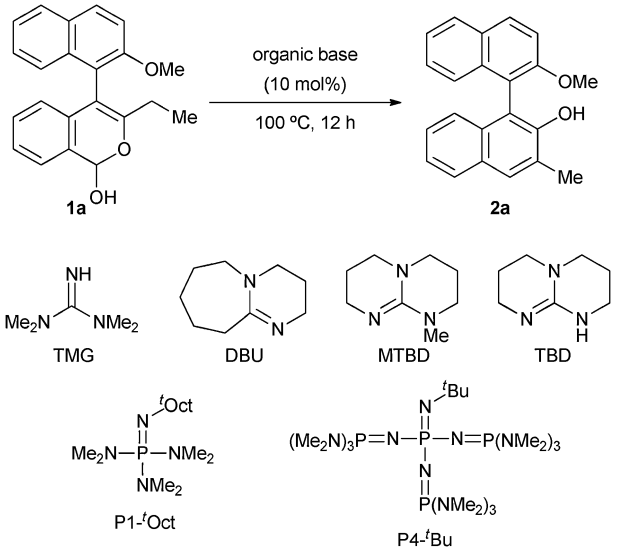
Scheme 1 Intramolecular multi-step transformation for the preparation of unsymmetrically substituted biaryl compounds.

We began by investigating the multi-step transformation of lactol **1a** catalyzed by 10 mol% of an organic base in DMSO at 100 °C for 12 h. As shown in Table 1, catalytic efficiency was mostly dependent on the basicity of the organic base employed (entries 1–6)[6] in the exception of TBD (entry 4). Among the organic bases tested, the strongest base, P4-^{t}Bu phosphazene base, accelerated the reaction efficiently (entry 6). It is noteworthy that TBD functioned as an adequate catalyst, giving rise to desired biaryl product **2a** in good yield (entry 4), and the yield was comparable to that of much stronger base, P4-^{t}Bu. In contrast, the reaction catalyzed by MTBD

[a] *Department of Chemistry, Graduate School of Science, Tohoku University, Aoba-ku, Sendai 980-8578, Japan. E-mail: mterada@m.tohoku.ac.jp; Fax: +81-22-795-6602; Tel: +81-22-795-6602*
[b] *Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Aoba-ku, Sendai 980-8578, Japan*

† Electronic supplementary information (ESI) available: Representative experimental procedure, spectroscopic data for lactols **1**, biaryl products **2**, and binaphthol derivative **4**. See DOI: 10.1039/c2cc31594g

Table 1 Intramolecular multi-step transformation of lactol **1a** catalyzed by organic bases[a]



Entry	Base	pK_{BH^+} [b]	Solvent	Yield (%)[c]
1	TMG	23.3	DMSO	25
2	DBU	24.3	DMSO	36
3	MTBD	25.5	DMSO	46
4	TBD	26.0	DMSO	80
5	P1-^{t}Oct	27.0[d]	DMSO	43
6	P4-^{t}Bu	42.7	DMSO	84
7	TBD		CH_3CN[e]	81
8	TBD		THF[e]	Quant. (90)[f]
9	P4-^{t}Bu		THF[e]	Quant. (94)[f]

[a] Unless otherwise noted, all reactions were carried out using 10 mol% of base at 100 °C for 12 h. [b] pK_{BH^+} in CH_3CN. [c] ^{1}H NMR yield. Remaining mass was recovered as unchanged **1a**. [d] pK_{BH^+} of P1-^{t}Bu. [e] The reactions were conducted in a sealed-tube. [f] Isolated yield.

(7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) and P1-^{t}Oct phosphazene bases, both having similar basicity to TBD, afforded product **2a** in modest yields under the same reaction conditions (entries 3 and 5). Further screening for other solvents revealed that MeCN and THF were also useful in the present intramolecular reaction (entries 7–9). In THF, both TBD and P4-^{t}Bu phosphazene bases acted as excellent catalysts to give **2a** in high yields (entries 8 and 9).

As shown in Table 1, TBD functioned as a unique catalyst in the present intramolecular multi-step transformation. The catalytic efficiency of TBD is comparable to that of P4-^{t}Bu despite the fact that TBD is much less basic than P4-^{t}Bu. Other organic bases that possess similar basicity to TBD, such as MTBD and P1-^{t}Oct, exhibited less catalytic activity than TBD. The observed unique catalysis by TBD would stem from the fact that TBD has both hydrogen-bond acceptor and donor sites in close proximity at the 5- and 7-position of nitrogen atoms, respectively. This characteristic feature is not available in the other organic bases employed. A plausible mechanism for the unique catalysis by TBD is depicted in Fig. 1 on the basis of the formation of two antiparallel hydrogen bonds.[7] Although at the initial step, the ring opening of lactol **1** to generate intermediary enolate **B** should be energetically unfavorable, the double hydrogen-bonding interaction between **1** and TBD would aid the smooth formation of

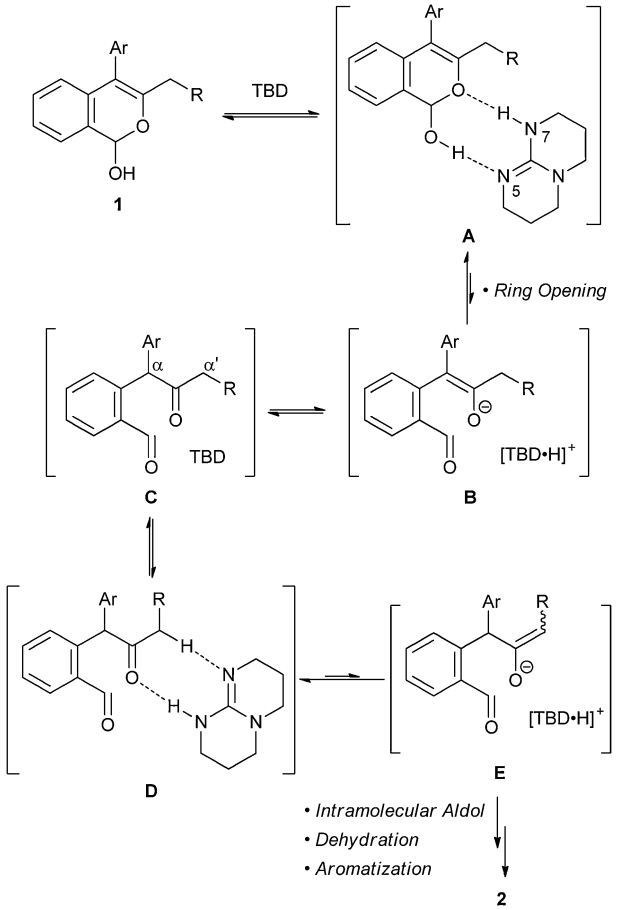
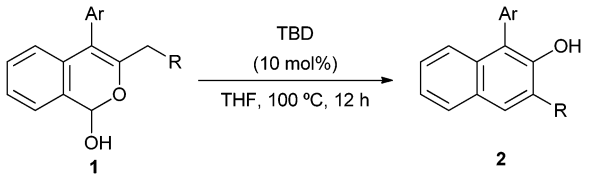


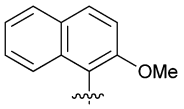
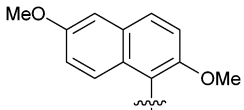
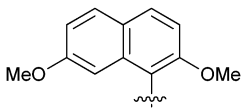
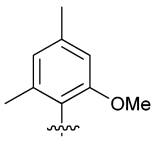
Fig. 1 Plausible reaction mechanism using TBD as the base catalyst.

ring-opened enolate **B** through antiparallel hydrogen-bonding model **A**. This consideration is also applicable to the formation of thermodynamically unfavorable regioisomeric enolate **E** from keto aldehyde **C**, where the acidity at the α′-position of **C** would be lower than that at the α-position because of the α-carbon bearing two aryl groups. This unfavorable process would be accelerated through the double hydrogen-bonding interaction between **C** and TBD, as shown in model **D**. Thus, *N*-methyl TBD (MTBD), having not only similar basicity but also structural resemblance to TBD, exhibited lower catalytic activity (Table 1, entry 3 *vs.* 4). It seems that the formation of the two antiparallel hydrogen bonds is the key to achieving the high catalytic performance. Further transformation of intermediary enolate **E** into biaryl compound **2** would be also promoted by the formation of the two hydrogen bonds when TBD was used as the catalyst.

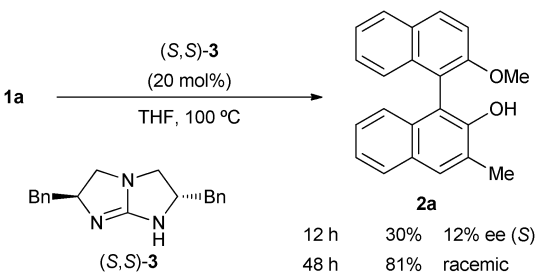
Having identified the suitable reaction conditions and the catalytic potential of TBD, we next investigated the substrate scope of the present intramolecular multi-step transformation (Table 2). Both linear and branched alkyl groups were well tolerated as the substituents (R) at the 3-position of desired product **2** (entries 1 and 2). In the present TBD-catalyzed reaction, heteroatoms, such as oxygen and sulfur, could also be introduced at the 3-position of product **2** (entries 3 and 4). 6- and 7-Methoxy-substituted binaphthyl products **2f** and **2g** were also obtained in excellent yields (entries 5 and 6). Furthermore, the reaction of lactol **1h** having a substituted phenyl group,

Table 2 Substrate scope of TBD-catalyzed intramolecular multi-step transformation of **1**[a]



Entry	1	Ar	R	2	Yield (%)[b]
1	**1b**		^{n}Pr	**2b**	96
2	**1c**	”	^{i}Pr	**2c**	82
3	**1d**	”	OMe	**2d**	83
4	**1e**	”	SMe	**2e**	79
5	**1f**		Me	**2f**	99
6	**1g**		Me	**2g**	98
7	**1h**		Me	**2h**	96

[a] Unless otherwise noted, all reactions were carried out using 10 mol% of TBD at 100 °C for 12 h in THF (0.2 M) in a sealed tube. [b] Isolated yield.



Scheme 2 Enantioselective intramolecular multi-step transformation catalyzed by chiral guanidine **3**.

instead of the naphthyl group, was demonstrated to emphasize the potential utility of the present method (entry 7).

Finally, we attempted the enantioselective catalysis of the present multi-step transformation using chiral bicyclic guanidine **3**.[8] The reaction of **1a** was investigated in the presence of 20 mol% of (*S*,*S*)-**3**. As shown in Scheme 2, under the optimal reaction conditions (THF, 100 °C, 12 h), the catalytic reaction of **1a** was sluggish, affording optically active product **2a** in low yield with low enantioselectivity. Prolonging the reaction time led to a disappointing result in terms of enantioselectivity, furnishing racemic product **2a**, although the chemical yield of **2a** could be improved. These results imply that optically active **2a** was racemized under the reaction conditions.‡ We therefore turned our attention to the synthesis of the optically active biaryl compound through the optical resolution of racemic **2a** using chiral diamine.[9] After the deprotection of methyl ether of **2a** by BBr_3, thus obtained racemic binaphthol derivative **4** was recrystallized from toluene in the presence of (*S*,*S*)-1,2-diphenyl-1,2-ethanediamine (**5**). (*R*)-**4** having 95% ee was recovered from the crystalline complex composed of (*R*)-**4** and (*S*,*S*)-**5** in 22% yield, after decomposition of the complex with dilute hydrochloric acid.

In conclusion, we have demonstrated an efficient method for the synthesis of unsymmetrically substituted 2,2′-dihydroxy-1,1′-biaryl compounds starting from lactol derivatives through the intramolecular multi-step transformation. TBD functioned as an efficient and unique catalyst presumably due to the formation of the antiparallel hydrogen bonds between TBD and (intermediary) substrates. Further studies of the design of reaction systems and chiral organic base catalysts are in progress with the aim of achieving the enantioselective synthesis of axially chiral biaryl compounds.

This work was partially supported by a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from MEXT, Japan. We gratefully acknowledge Professors T. Ooi and D. Uraguchi (Nagoya University) and Dr Y. Nakamura and Mr T. Takeda (Daiichi Sankyo Co., Ltd.) for HRMS analysis.

Notes and references

‡ Optically active **4** was racemized in the presence of TBD (10 mol%) in THF at 100 °C. See ESI† for details.

1 For reviews of enantioselective catalysis with BINOL derivatives, see: (*a*) L. Pu, *Chem. Rev.*, 1998, **98**, 2405; (*b*) Y. Chen, S. Yekta and A. K. Yudin, *Chem. Rev.*, 2003, **103**, 3155; (*c*) J. M. Brunel, *Chem. Rev.*, 2005, **105**, 857; (*d*) M. Terada, *Synthesis*, 2010, 1929.
2 For reviews, see: (*a*) P. Kočovský, S. Vyskočil and M. Smrčina, *Chem. Rev.*, 2003, **103**, 3213; (*b*) M. Shibasaki and S. Matsunaga, *Chem. Soc. Rev.*, 2006, **35**, 269.
3 H. Egami, K. Matsumoto, T. Oguma, T. Kunisu and T. Katsuki, *J. Am. Chem. Soc.*, 2010, **132**, 13633 and references cited therein.
4 X. Shen, G. O. Jones, D. A. Watson, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 11278 and references cited therein.
5 R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1455.
6 (*a*) T. Rodima, I. Kaljurand, A. Pihl, V. Mäemets, I. Leito and I. A. Koppel, *J. Org. Chem.*, 2002, **67**, 1873–1881; (*b*) I. Kaljurand, A. Kütt, L. Sooväli, T. Rodima, V. Mäemets, I. Leito and I. A. Koppel, *J. Org. Chem.*, 2005, **70**, 1019; (*c*) R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter, F. G. Bordwell, A. V. Satish, G.-Z. Ji, E.-M. Peters, K. Peters, H. Georg von Schnering and L. Walz, *Liebigs Ann.*, 1996, 1055.
7 For TBD as an efficient catalyst having donor–accepter property of hydrogen bonds, see: (*a*) L. Simón and J. M. Goodman, *J. Org. Chem.*, 2007, **72**, 9656; (*b*) A. Chuma, H. W. Horn, W. C. Swope, R. C. Pratt, L. Zhang, B. G. G. Lohmeijer, C. G. Wade, R. M. Waymouth, J. L. Hedrick and J. E. Rice, *J. Am. Chem. Soc.*, 2008, **130**, 6749; (*c*) Also see: W. Ye, J. Xu, C.-T. Tan and C.-H. Tan, *Tetrahedron Lett.*, 2005, **46**, 6875(*d*) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wong and C.-H. Tan, *Angew. Chem., Int. Ed.*, 2009, **48**, 3627–3631.
8 (*a*) W. Ye, D. Leow, S. L. M. Goh, C.-T. Tan, C.-H. Chian and C.-H. Tan, *Tetrahedron Lett.*, 2006, **47**, 1007; (*b*) J. Shen, T. T. Nguyen, Y.-P. Goh, W. Ye, X. Fu, J. Xu and C.-H. Tan, *J. Am. Chem. Soc.*, 2006, **128**, 13692; (*c*) Also see: E. J. Corey and M. J. Grogan, *Org. Lett.*, 1999, **1**, 157.
9 (*a*) M. Kawashima and R. Hirata, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2002; (*b*) Also see: D. Cai, D. L. Hughes, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1995, **36**, 7991.