Advanced Synthesis & Catalysis

Accepted Article

Title: Asymmetric Synthesis of Dihydronaphthalene-1,4-diones via Carbene-Catalyzed Stereodivergent Reaction

Authors: Xinqiang Fang, Shuang Yang, Zhifei Zhao, Shouang Lan, jinggong liu, and Shuhua Liu

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900506

Link to VoR: http://dx.doi.org/10.1002/adsc.201900506

10.1002/adsc.201900506

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Asymmetric Synthesis of Dihydronaphthalene-1,4-diones via Carbene-Catalyzed Stereodivergent Reaction

Zhifei Zhao,[a] Shuang Yang,[a] Shouang Lan,[a] Jinggong Liu,[c] Shuhua Liu,[b]* and Xinqiang Fang[a]*

[a] State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, University of Chinese Academy of Sciences, Fuzhou, Fujian, 350002, China. Email: xqfang@fjirsm.ac.cn
[b] Shandong Analysis and Test Center, Qilu University of Technology (Shandong Academy of Sciences), Jinan, 250014, China. Email: liushuhuaosso@126.com
[c] Orthopedics Department, Guangdong Provincial Hospital of Traditional Chinese Medicine, NO. 111 Dade Road, Guangzhou 510120, China

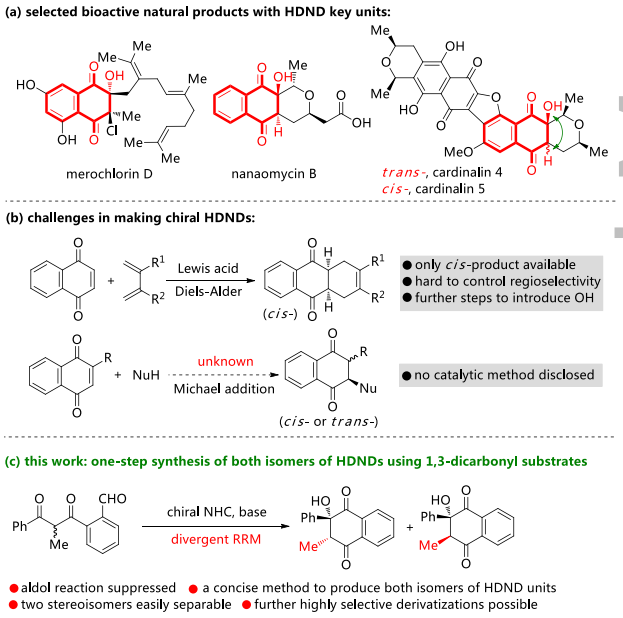
Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. 2-Hydroxy-2,3-dihydronaphthalene-1,4-diones (HDNDs) are ubiquitous in natural products and bioactive molecules, but the rapid asymmetric construction of such scaffolds remains a significant challenge to date. Reported herein is the rapid construction of the above key units via carbene-catalyzed benzoin reaction. The resolution technique of divergent reaction on racemic mixture (divergent RRM) was employed, affording both isomers of HDNDs in a one-step fashion. Disubstituted substrates afford products with two contiguous quaternary stereocenters. A series of highly selective transformations on the products can be realized, and mechanistic studies indicate that the benzoin reaction is much faster than the racemization process and the aldol reaction.

Keywords: umpolung, cyclization, carbene, kinetic resolution

2-Hydroxy-2,3-dihydronaphthalene-1,4-diones (HDNDs) widely exist in naturally occurred substances such as merochlorin D, nanaomycin B, cardinalin 4, and cardinalin 5, and they display promising bioactivities like antibacterial activity and antimicrobial activity (Scheme 1a).[1] Noteworthy is that cardinalin 4 and cardinalin 5 are diastereomeric isomers and show different activities.[1h] However, protocols that can rapidly construct chiral HDNDs remain scarce. Asymmetric Diels-Alder reactions between naphthalene-1,4-diones and 1,3-dienes have been used to assemble *cis*-HDNDs, but the regioselectivity of the reaction is hard to be controlled when diene substituents are different, and more steps are needed to introduce hydroxyl groups (Scheme 1b).[2] Asymmetric Michael addition of a nucleophile to substituted naphthalene-1,4-diones constitutes a good choice to make HDNDs, but such approach remains unknown to the best of our knowledge (Scheme 1b). Furthermore, the synthesis of *cis*- and *trans*-HDNDs usually employ different sets of reaction conditions or retrosynthetic plans, thus making the existing synthetic methods highly costly and time-consuming.[3] Therefore, developing a concise approach to afford both diastereomers of HDNDs still remains a formidable challenge to date.



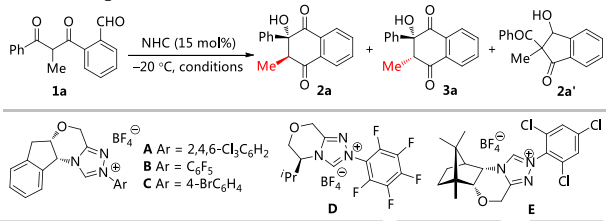
Scheme 1. Background and Work Hypothesis.

N-heterocyclic carbene (NHC)-catalyzed asymmetric benzoin reaction has proven to be a powerful approach to produce *α*-hydroxyketones via C-C bond formation.[4] A recent increasing research interest has been paid to the development of methods leading to benzoin products with multiple stereocenters, as reported by Ema and Johnson's groups.[5] During the past three years, we have employed the idea of group addition-kinetic resolution (GAKR) to systematically study the

benzoin reactions using racemic substrates. In more details, through rational additions of substituted groups into the nonchiral/prochiral benzoin reaction substrates, and running the corresponding catalytic kinetic resolutions, we were able to provide a series of tetralones, rotenoids, chromanones, and flavanones with multiple stereocenters in a one-step fashion.[6] Classical kinetic resolution (KR), dynamic kinetic resolution (DKR), and divergent RRM were all tolerated by the above benzoin reactions, and all these have extended greatly the applications of this named reaction, and a series of new insights have also been disclosed. As the last work of this series, we report herein the rapid access to both stereoisomers of HDNDs via benzoin reaction-mediated divergent RRM using 2-substituted 1,3-diketones with a formylphenyl group (Scheme 1c).

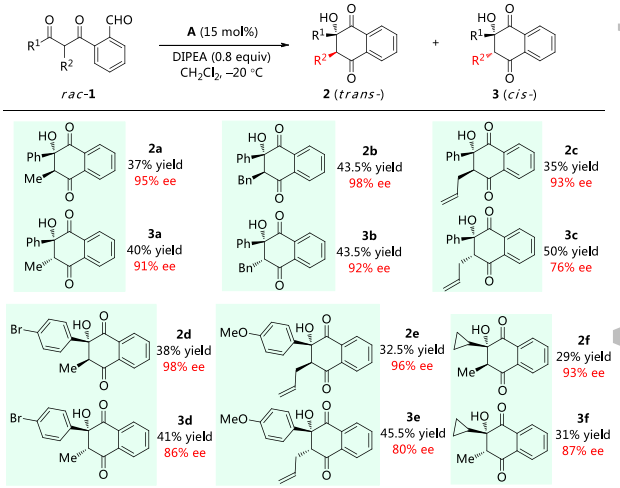
We commenced by selecting *rac*-**1a** as the model substrate. Catalyst **A**[7a] and stoichiometric K_2CO_3 were used initially (Table 1, entry 1). However, aldol product **2a'** was obtained in 35% yield and two diastereomeric products **2a** and **3a** were obtained in 22% and 30% yields with 85% and 69% ee, respectively (Table 1, entry 1). Somewhat to our surprise, the result did not support a DKR pathway,[8] and divergent RRM was applicable. Although the yield is 50% theoretically, the technique of divergent RRM is advantageous in providing diversified products and shortening the synthetic routes.[9] Selected applications of this technique can be found in the total synthesis of (-)-cyanthiwigin G/(+)-cyathin A_3,[10a] rotigotine/(*S*)-8-OH-DPAT,[10b] (+)-erogorgiaene/(-)-colombiasin A,[10c-d] and sanggenon C/sanggenon O,[10e] etc. In all these cases, the technique of divergent RRM proved to be the best choices in making the above structurally related pairs of natural products. To our pleasure, in our reaction both stereoisomeric products are easily separable and this method provides an approach for the rapid synthesis of both *cis*- and *trans*-isomers of HDNDs, which will be useful in making both isomers of related bioactive molecules.[1h] Then we tried to suppress the aldol side product, a perennial problem among intramolecular benzoin reaction-related studies in the past decades.[11] Similar results with that in entry 1 were observed when catalytic amount of K_2CO_3 was used (Table 1, entry 2), and catalysts **B**,[7b] **C**, and **D**[7c] all led to the generation of aldol product together with two diastereomeric products with various yields and ee values (Table 1, entries 3–5). Using catalyst **A**, we surveyed a series of bases. Cs_2CO_3 and K_3PO_4 resulted in more than 20% yield of aldol product (Table 1, entries 6 and 7), and weaker base of $KHCO_3$ delivered less **2a'** (Table 1, entry 8). Organic bases such as DBU and Et_3N were not good choices (Table 1, entries 9 and 10), but $^iPr_2NEt$ proved suitable considering both the yields and ee of the two products (Table 1, entry 11). While the solvent of toluene was not superior (Table 1, entry 12), CH_2Cl_2 could further diminish the formation of **2a'** (Table 1, entry 13). Finally we found that increasing the amount of $^iPr_2NEt$ can promote the enantioselectivities to an excellent level without increasing the amount of aldol product (Table 1, entry 14). Under the optimal conditions, catalyst **E**[4y] was also surveyed but only resulted in the formation of **2a'** (Table 1, entry 15).

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	base (equiv), solvent	yield (%) 2a/3a/2a'	ee (%) 2a/3a
1	**A**	K_2CO_3 (1.0), THF	22/30/35	85/69
2	**A**	K_2CO_3 (0.2), THF	28/32/21	87/73
3	**B**	K_2CO_3 (0.2), THF	16/50/15	72/18
4	**C**	K_2CO_3 (0.2), THF	17/18/51	87/80
5	**D**	K_2CO_3 (0.2), THF	16/57/14	60/17
6	**A**	Cs_2CO_3 (0.2), THF	28/28/24	80/78
7	**A**	K_3PO_4 (0.2), THF	22/43/23	95/72
8	**A**	$KHCO_3$ (0.2), THF	26/40/15	98/67
9	**A**	DBU (0.2), THF	34/40/12	91/77
10	**A**	Et_3N (0.2), THF	25/42/15	91/56
11	**A**	$^iPr_2NEt$ (0.2), THF	38/38/6	93/90
12	**A**	$^iPr_2NEt$ (0.2), toluene	31/45/10	87/75
13	**A**	$^iPr_2NEt$ (0.2), CH_2Cl_2	36/43/4	98/85
14	**A**	$^iPr_2NEt$ (0.8), CH_2Cl_2	**37/40/3**	**95/91**
15	**E**	$^iPr_2NEt$ (0.8), CH_2Cl_2	-/-/96	N.D.[b]

[a] Reaction conditions: **1a** (0.1 mmol), NHC (0.015 mmol), solvent (1.5 mL), −20 °C, under argon atmosphere. All yields are isolated yields and were based on **1a**; ee values were determined via HPLC analysis on a chiral stationary phase. [b] Not determined.



[a] Reaction conditions: *rac*-**1** (0.1 mmol), **A** (0.015 mmol), CH_2Cl_2 (1.5 mL), −20 °C, under argon atmosphere. All yields are isolated yields and were based on *rac*-**1**; ee values were determined via HPLC analysis on a chiral stationary phase.

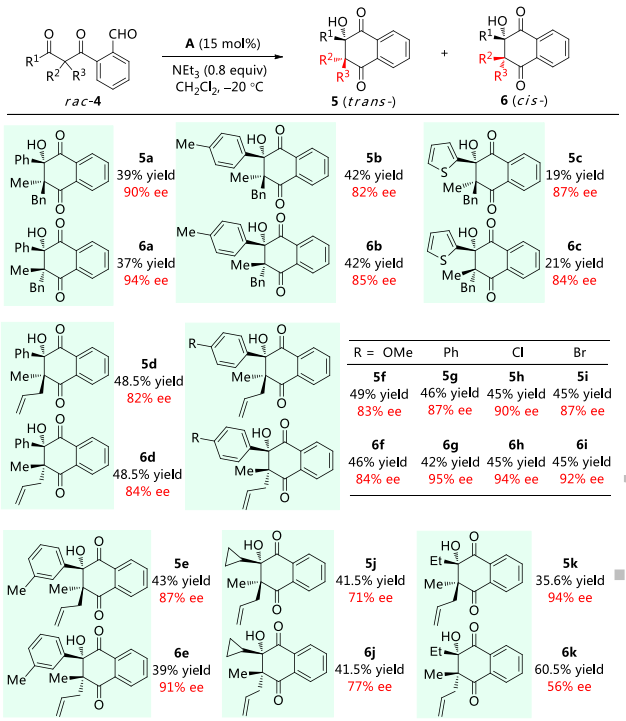
Scheme 2. Substrate Scope of Monosubstituted Diketones.[a]

10.1002/adsc.201900506

Having established the optimal conditions, we then checked a series of mono-substituted diketone substrates. The replacement of Me group in **2a** by Bn did not affect the results (Scheme 2, **2b**/**3b**), and 2-allyl diketone was also tolerated (Scheme 2, **2c**/**3c**). We then tested differently substituted phenyl ketones, and found that the annulation products were produced in good yields with good to excellent enantioselectivities (Scheme 2, **2d**/**3d**, and **2e**/**3e**). Furthermore, aliphatic ketone also worked well considering the stereoselectivity, albeit with moderate total yield (Scheme 2, **2f**/**3f**). The configuration of **2a** was confirmed via single crystal X-ray structure analysis (Figure 1).[12]

Furthermore, we studied substrates with fully substituted carbon centers. As shown in Scheme 3, Bn/Me-disubstituted diketones worked well under slightly modified conditions (using Et_3N instead of $^iPr_2NEt$), affording the corresponding stereoisomers in moderate to good yields with 82–94% ee (Scheme 3, **5a**/**6a**, **5b**/**6b**, and **5c**/**6c**). The absolute configuration of **5c** was determined via single crystal X-ray structure analysis (Figure 1).[12] We then studied a series of substrates with allyl/Me substituents. Phenyl-substituted diketone could release **5d** and **6d** with good ee values (Scheme 3, **5d** and **6d**), and the introduction of electron-rich 3-Me or 4-OMe substituents into the phenyl group had no influence on the outcomes (Scheme 3, **5e**/**6e**, and **5f**/**6f**). The phenyl ketone bearing electron-neutral phenyl group worked well to deliver the two isomers in good yields with high to excellent ee values (Scheme 3, **5g**/**6g**). Additionally, substrates with electron-poor Cl or Br group underwent smooth annulations to generate the corresponding products with 87–95% ee (Scheme 3, **5h**/**6h** and **5i**/**6i**). Aliphatic ketones with cyclopropyl group or ethyl group were also tolerated in this reaction, producing **5j**/**6j** and **5k**/**6k** in good total yield, albeit with moderate to excellent enantioselectivities (Scheme 3, **5j**/**6j** and **5k**/**6k**).

Gram-scale reaction proved possible using **1e** (1.5 g) as the example, without obvious erosion of yields and ee values of the products (Scheme 4a). Making all four isomers of a molecule with multiple stereocenters is highly needed in drug discovery since different physiological and pharmacological activities might be derived from different isomers.[13] In this work, using divergent RRM, all four stereoisomers of the products can be easily accessed using **A** and *ent*-**A** as the catalysts through two reactions (Scheme 4b). Further transformations based on product **2e** can also be easily realized (Scheme 4c). For instance, selective reduction of **2e** using $NaBH_4$ afforded **7a** in 84% yield with 97% ee, and the full reduction of **2e** produced **7b** with four contiguous stereocenters. Additionally, nucleophilic attack of **2e** by vinyl magnesium bromide allowed access to diol **7c** without erosion of the ee value.[14]



[a] Reaction conditions: *rac*-**4** (0.1 mmol), **A** (0.015 mmol), CH_2Cl_2 (1.5 mL), −20 °C, under argon atmosphere. All yields are isolated yields and were based on *rac*-**4**; ee values were determined via HPLC analysis on a chiral stationary phase.

Scheme 3. Substrate Scope of 2,2-Disubstituted Diketones.

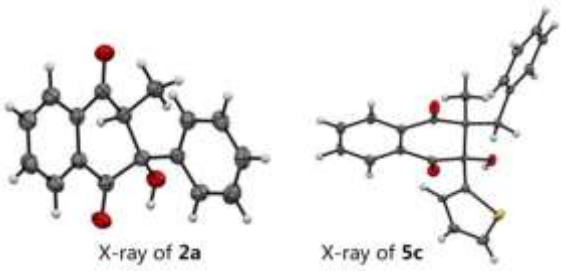
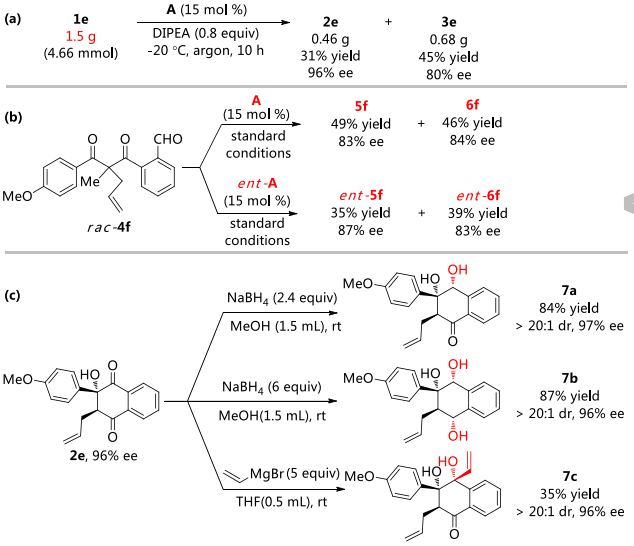
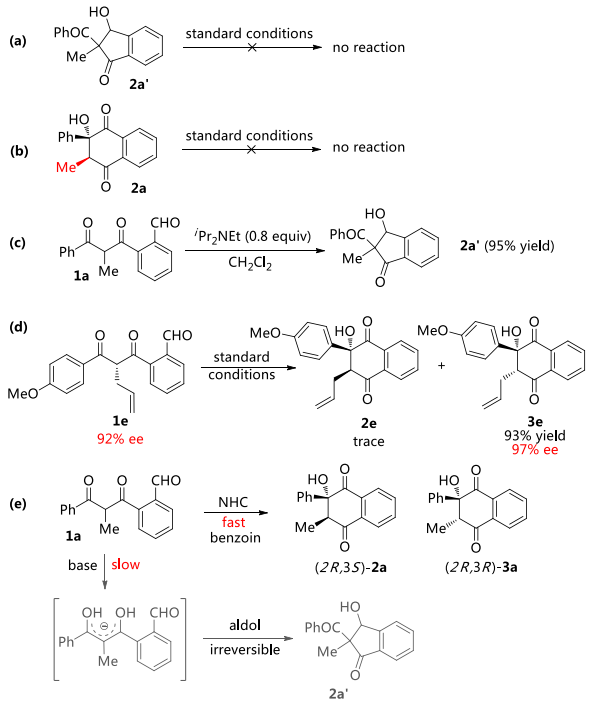


Figure 1. X-ray Structures of **2a** and **5c**.



Scheme 4. Synthetic Applications.

To further demonstrate the mechanistic details of this process, especially the reactions using mono-substituted 1,3-diketones, we conducted further studies. First, thoroughly different to the prior DKR reaction,[6b] the aldol product **2a'** could not be converted to benzoin product via reversible process (Scheme 5a). Moreover, no isomerization of **2a** to **3a** occurred under the standard conditions (Scheme 5b). Noteworthy is that 95% yield of the aldol product was formed without NHC catalyst (Scheme 5c), showing that the deprotonation-racemization process can occur. However, when enantioenriched substrate **1e** was put under the standard conditions, **3e** was obtained in 93% yield with 97% ee, indicating that the benzoin process happens much faster than the racemization step (Scheme 5d). It's a surprising observation because aldol type side reactions have been really difficult to be suppressed using easily enolizable substrates,[11] and 1,3-diketone type substrates have been widely used in DKR reactions.[8] Summarily, a plausible mechanism was proposed in Scheme 5e. In the whole process, the benzoin reaction happens much faster than the racemization and aldol process, and both aldol and benzoin reactions are irreversible. This mechanism is sharply different to the previous reports.[6b]



Scheme 5. Mechanistic Studies.

In conclusion, we have provided a solution to the long-term challenge of making the key units of HDNDs in a concise fashion through NHC-catalyzed benzoin reaction. Both *cis*- and *trans*-products could be delivered in a one-step approach with good to excellent enantioselectivities, and all four stereoisomers can be accessed. A series of highly selective transformations on the products can be easily achieved. Furthermore, the mechanistic studies disclosed that the benzoin process is much faster than the racemization step, and an irreversible aldol reaction was also demonstrated. We have shown that the idea of group addition-kinetic resolution (GAKR) is useful in further promoting the applications and values of benzoin reaction. More utilities of GAKR in other named reactions will be conducted.

Experimental Section

General procedure for benzoin reaction of *rac*-1: To a dried 10 mL Schlenk tube equiped with a tiny magnetic stir bar, catalyst **A** (7.2 mg, 15 mol%), *rac*-**1** (0.1 mmol), and DIPEA (0.08 mmol, 13.2 uL) were added together. The flask was then evacuated and refilled with dry argon. To this mixture, CH_2Cl_2 (1.5 mL) was added and the resulting solution was stirred at −20 ºC for 3−5 h. After completion of the reaction, solvent was evaporated and the resulting crude products were purified through a short column chromatography on silica gel with ethyl acetate and petroleum ether as eluent to afford the desired product **2** and **3**.

General procedure for benzoin reaction of *rac*-4: To a dried 10 mL Schlenk tube equiped with a tiny magnetic stir bar, catalyst **A** (7.2 mg, 15 mol%), *rac*-**4** (0.1 mmol), and Et_3N (0.08 mmol, 11.1 uL) were added together. The flask was then evacuated and refilled with dry argon. To this mixture, CH_2Cl_2 (1.5 mL) was added and the resulting solution was stirred at −20 ºC for 3−7 h. After completion of the reaction, solvent was evaporated and the resulting crude products were purified through a short column chromatography on silica gel with ethyl acetate and petroleum ether as eluent to afford the desired product **5** and **6**.

Acknowledgements

This work was supported by NSFC (21871260, 21502192 and 21402199), the strategic priority research program of the Chinese Academy of Sciences (XDB20000000), Fujian Natural Science Foundation (2018J05035), and China Postdoctoral Science Foundation (2018M630734). We thank Professor Daqiang Yuan for the X-ray data analysis.

References

[1] a) L. Kaysser, P. Bernhardt, S.-J. Nam, S. Loesgen, J. G. Ruby, P. Skewes-Cox, P. R. Jensen, W. Fenical, B. S. Moore, *J. Am. Chem. Soc.* **2012**, *134*, 11988; b) P. Bernhardt, T. Okino, J. M. Winter, A. Miyanaga, B. S. Moore, *J. Am. Chem. Soc.* **2011**, *133*, 4268; c) L. Kaysser, P. Bernhardt, S.-J. Nam, S. Loesgen, J. G. Ruby, P. Skewes-Cox, P. R. Jensen, W. Fenical, B. S. Moore, *J. Am. Chem. Soc.* **2014**, *136*, 14626; d) Z. Wu, S. Li, J. Li, Y. Chen, K. Saurav, Q. Zhang, H. Zhang, W. Zhang, W. Zhang, S. Zhang, C. Zhang, *Mar. Drugs* **2013**, *11*, 2113; e) C. Ito, Y. Kondo, K. S. Rao, H. Tokuda, H. Nishino, H. Furukawa, *Chem. Pharm. Bull.* **1999**, *47*, 1579; f) Y. Hori, Y. Abe, N. Shigematsu, T. Goto, M. Okuhara, M. Kohsaka, *J. Antibiot.* **1993**, *46*, 1890; g) T. Yoshitake, S. Masako, J. Wei, I. Jun, Y. Hiroshi, O. Satoshi, *J. Antibiot.* **1995**, *48*, 720; h) M. S. Buchanan, M. Gill, J. Yu, *J. Chem. Soc., Perkin Trans.* **1997**, *6*, 919.

[2] a) D. H. Ryu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 4800; b) D. Liu, E. Canales, E. J. Corey, *J. Am. Chem. Soc*. **2007**, *129*, 1498; c) Z.-Y. Han, D.-F. Chen, Y.-Y. Wang, R. Guo, P.-S. Wang, C. Wang, L.-Z. Gong, *J. Am. Chem. Soc.* **2012**, *134*, 6532; d) L. Albrecht, C. V. Gómez, C. B. Jacobsen, K. A. Jørgensen, *Org. Lett.* **2013**, *15*, 3010; e) D. A. Evans, J. Wu, *J. Am. Chem. Soc*. **2003**, *125*, 10162.

[3] a) S. Kamo, K. Yoshioka, K. Kuramochi, K. Tsubaki, *Angew. Chem. Int. Ed.* **2016**, *55*, 10317; b) S. A. Snyder, Z.-Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744; c) K. C. Nicolaou, G. Liu, K. Beabout, M. D. McCurry, Y. Shamoo, *J. Am. Chem. Soc.* **2017**, *139*, 3736.

[4] For selected reviews of NHC catalysis including benzoin reactions, see: a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534; b) X. Sun, J. Wu, *Chin. J. Org. Chem*. **2006**, *26*, 745; c) K. Zeitler, *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; d) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; e) N. Marion, S. Diez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; f) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, *42*, 55; g) J. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77; h) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182; i) H. U. Vora, T. Rovis, *Aldrichimica Acta* **2011**, *44*, 3; j) M. Qu, J. He, *Chin. J. Org. Chem.* **2011**, *31*, 1388; k) X. Bugaut, F. Glorius, *Chem. Soc. Rev*. **2012**, *41*, 3511; l) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 11686; m) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; n) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev*. **2015**, *115*, 9307; o) R. S. Menon, A. T. Biju, V. Nair, *Beilstein J. Org. Chem.* **2016**, *12*, 444; p) P. Haghshenas, S. M. Langdon, M. Gravel, *Synlett* **2017**, *28*, 542; q) K. Dzieszkowski, Z. Rafiński, *Catalysts* **2018**, *8*, 549. For selected reports of intramolecular benzoin reaction, see: r) Y. Hachisu, J. W. Bode, K. Suzuki, *Adv. Synth. Catal.* **2004**, *346*, 1097; s) D. Enders, O. Niemeier, G. Raabe, *Synlett* **2006**, 2431; t) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem. Int. Ed.* **2006**, *45*, 1463; u) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3492; v) H. Takikawa, K. Suzuki, *Org. Lett.* **2007**, *9*, 2713; w) Y. Li, Z. Feng, S.-L. You, *Chem. Commun.* **2008**, 2263; x) M.-Q. Jia, S.-L. You, *ACS Catal*. **2013**, *3*, 622; y) Z. Rafiński, A. Kozakiewicz, *J. Org. Chem.* **2015**, *80*, 7468.

[5] a) T. Ema, Y. Oue, K. Akihara, Y. Miyazaki, T. Sakai, *Org. Lett.* **2009**, *11*, 4866; b) C. G. Goodman, J. S. Johnson, *J. Am. Chem. Soc.* **2014**, *136*, 14698; c) T. Ema, Y. Nanjo, S. Shiratori, Y. Terao, R. Kimura, *Org. Lett.* **2016**, *18*, 5764; d) Y. Li, S. Yang, G. Wen, Q. Lin, G. Zhang, L. Qiu, X. Zhang, G. Du, X. Fang, *J. Org. Chem.* **2016**, *81*, 2763.

[6] a) G. Wen, Y. Su, G. Zhang, Q. Lin, Y. Zhu, Q. Zhang, X. Fang, *Org. Lett.* **2016**, *18*, 3980; b) G. Zhang, S. Yang, X. Zhang, Q. Lin, D. K. Das, J. Liu, X. Fang, *J. Am. Chem. Soc.* **2016**, *138*, 7932; c) L. Vasamsetty, X. Kong, M. Meng, S. Yang, W. Xu, P. S. Reddy, X. Fang, *Chem. Asian J.* **2018**, *13*, 3838; d) S. Perveen, S. Yang, M. Meng, W. Xu, G. Zhang, X. Fang, *Comms. Chem.* **2019**, *2*: 8; e) W. Xu, Y. Li, R. Liu, S. Yang, J. Liu, X. Fang, *Org. Chem. Front.* **2019**, *6*, 290; f) S. T. Zehra, G. Zhang, S. Yang, X. Fang, *Org. Biomol. Chem.* **2019**, *17*, 2169.

[7] a) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094; b) M. S. Kerr, T. Rovis, *J. Am. Chem. Soc*. **2004**, *126*, 8876; c) K. Thai, S. M. Langdon, F. Bilodeau, M. Gravel, *Org. Lett.* **2013**, *15*, 2214; d)

[8] For selected reviews of 1,3-dicarbonyl compounds-participated DKR reactions, see: a) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36; b) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475; c) F. F. Huerta, A. B. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321; d) M.-J. Kim, Y. Ahn, J. Park, *Curr. Opin. Biotechnol.* **2002**, *13*, 578; e) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291; f) H. Pellissier, *Tetrahedron* **2008**, *64*, 1563; g) J. Steinreiber, K. Faber, H. Griengl, *Chem. Eur. J.* **2008**, *14*, 8060; h) H. Pellissier, *Tetrahedron* **2011**, *67*, 3769.

[9] For the selected reviews on the divergent reactions on racemic mistures, see: a) L. C. Miller, R. Sarpong, *Chem. Soc. Rev.* **2011**, *40*, 4550; b) J. R. Dehli, V. Gotor, *Chem. Soc. Rev*. **2002**, *31*, 365; c) H. B. Kagan, *Tetrahedron* **2001**, *57*, 2449; d) *Separation of Enantiomers*; M. Todd, Ed.; Wiley-VCH Verlag & Co. KGaA; Weinheim; 2014.

[10] a) L. C. Miller, J. M. Ndungu, R. Sarpong, *Angew. Chem., Int. Ed.* **2009**, *48*, 2398; b) R. Webster, A. Boyer, M. J. Fleming, M. Lautens, *Org. Lett.* **2010**, *12*, 5418; c) H. M. L. Davies, A. M. Walji, *Angew. Chem., Int. Ed.* **2005**, *44*, 1733; d) H. M. L. Davies, X. Dal, M. S. Long, *J. Am. Chem. Soc*. **2006**, *128*, 2485; e) C. Qi, Y. Xiong, V. Eschenbrenner-Lux, H. Cong, J. A. Porco, Jr. *J. Am. Chem. Soc.* **2016**, *138*, 798.

[11] a) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem. Int. Ed.* **2006**, *45*, 1463; b) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3492; c) H. Takikawa, K. Suzuki, *Org. Lett.* **2007**, *9*, 2713; d) Y. Li, Z. Feng, S.-L. You, *Chem. Commun.* **2008**, 2263.

[12] CCDC 1576285 (**2a**) and CCDC 1576286 (**5c**) contain the supplementary crystallographic data for this paper. These data can be obtained from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] a) *Drug Stereochemistry: Analytical Methods and Pharmacology*, ed. K. Jozwiak, W. J. Lough and I. W. Wainer, Informa, New York, 2012; b) *Foye's Principles of Medicinal Chemistry*, ed. T. L. Lemke, D. A. Williams, V. F. Roche and S. W. Zito, Lippincott Williams & Wilkins, Wolters Kluwer, Baltimore, 2013.

[14] J. G. Allen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 351.

10.1002/adsc.201900506

COMMUNICATION

Asymmetric Synthesis of Dihydronaphthalene-1,4-diones via Carbene-Catalyzed Stereodivergent Reaction

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Zhifei Zhao,[a] Shuang Yang,[a] Shouang Lan,[a] Jinggong Liu,[c] Shuhua Liu,[b]* and Xinqiang Fang[a]*