A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Chiral phosphoric acid-catalyzed asymmetric synthesis of hetero-triarylmethanes from racemic indolyl alcohols

Authors: Caizhen Yue, Fei Na, Xiantao Fang, Cao Yang, and Jon Antilla

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201804330
Angew. Chem. 10.1002/ange.201804330

Link to VoR: http://dx.doi.org/10.1002/anie.201804330
http://dx.doi.org/10.1002/ange.201804330

WILEY-VCH

10.1002/anie.201804330

COMMUNICATION

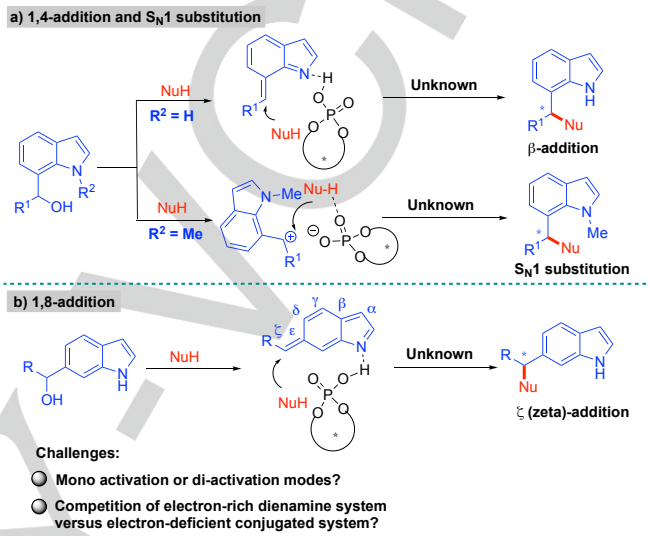
WILEY-VCH

Chiral phosphoric acid-catalyzed asymmetric synthesis of hetero-triarylmethanes from racemic indolyl alcohols **

Caizhen Yue, Fei Na, Xiantao Fang, Yang Cao and Jon C. Antilla* [a]

Abstract: *The direct enantioselective 1,4- and 1,8-arylations of 7-methide-7H-indoles and 6-methide-6H-indoles, generated in-situ from diarylmethanols with electron-rich arenes as nucleophiles, has been achieved in the presence of chiral phosphoric acids (CPA's). These two remote activation protocols provide an efficient approach for the construction of diverse hetero-triarylmethanes in high yields (up to 97%) and with excellent enantioselectivities (up to 96%). Mechanistically inspired experiments tentatively indicate that the catalytic enantioselective 1,4-addition as well as the formal S_N1 substitution could proceed efficiently in the similar catalytic systems. Furthermore, the modification of catalytic system and diarylmethanol structure successfully deviates the reactivity toward a remote highly enantioselective 1,8-arylation reaction. This flexible activation mode and novel reactivity of diarylmethanols expand the synthetic potential of chiral phosphoric acids.*

Optically active hetero-triarylmethanes are very important structural motifs in natural products, biological active molecules and synthetic materials.[1] Therefore, the development of efficient strategies for enantioenriched hetero-triarylmethane derivatives is of great interest to the synthetic community. Diarylmethanols have emerged as versatile precursors for the construction of hetero-triarylmethane derivatives.[2] The racemic alcohols used can be easily converted to active intermediates, such as quinone methides (QMs) or carbocationic species, via an acid-catalyzed dehydration pathway. Recently, great achievements have been made in the catalytic asymmetric 1,4-additions and formal S_N1 substitutions of diarylmethanols to deliver hetero-triarylmethanes. As a result, various activation patterns have been successfully documented, such as bi-functional modes,[3] coordination catalysis[4] and dual ion-pairing modes.[5] however, the enantioselective transformations based on the more challenging mono-activation mode still remain unexplored. Therefore, a direct and broadly applicable synthetic strategy for this important structural motif would be highly valuable. On the basis of the asymmetric additions to diarylmethanols, we report herein a unique 1,4-addition reaction of electron-rich arenes to *in situ* generated 7-methide-7*H*-indoles from the 7-indolylmethanols by employing a CPA as the catalyst. (Scheme 1a) This transformation relies upon the CPA catalyzed *in situ* generation of the active 6-methide-6*H*-indoles[2e,6] and the remote activation by non-covalent hydrogen bonding between the imines and the acidic proton of the CPA.



Scheme 1. Possible reaction pathways and activation modes of diarylmethanols.

This addition process proceeds with a broad substrate scope in terms of nucleophiles diversity, for example indoles and *N*-protected indoles; especially the less nucleophilic pyrrole series are tolerated. Consequently, a mono activation mechanism is a possible explanation for the stereochemical outcome of this 1,4-addition reaction.[7] The novel reactivity of the indolyl alcohols is probably owing to the formation of the particular 10π-electron aromatic structure. Moreover, The MeO and NH groups in the 7-indolylmethanols contribute to stabilize the 6-methide-6*H*-indoles or carbocation species could be beneficial for stereoselectivity.[8] Having noticed the unique reactivity of the designed 7-indolylmethanol, we expect that this strategy could be further applied to the remote stereoinduction.

Inspired by recent success in the remote stereocontrol[9], we envisioned the possibility to pursue the unusual 1,8-addition[10] with this strategy (Scheme 1b). Despite its important synthetic significance in the modern organic synthesis, direct enantioselective 1,8-additions have been far less exploited.[11] This is probably due to the difficulties in the design and synthesis of the proper 1,8-acceptors. In addition, the polyelectrophilic nature of 1,8-addition acceptors increases reaction complexity. More importantly, the lack of efficient catalytic system and activation mode further limits the development of the new *ζ* (zeta)-stereocenter. To the best of our knowledge, there are only two examples[12] covering the catalytic asymmetric 1,8-addition reactions, which employed ζ-substituted trienyl *N*-acylpyrroles and *p*-QMs as electrophiles. It is noteworthy that; 1) the two cases mentioned above all rely on a bi-functional activation mode[13] and 2) the activation of 1,8-addition acceptors don't involve the geometric control. Based on these studies and our previous efforts in phosphoric acid catalysis,[14] we herein document a novel CPA catalyzed asymmetric 1,8-addition of electron-rich

[a] Caizen Yue, Fei Na, Xiantao Fang, Yang Cao and Prof. Dr. Jon C. Antilla
Institute for Molecular Design and Synthesis
School of Pharmaceutical Science and Technology
Health Science Platform
Tianjin University, Tianjin 300072 (China)
E-mail: jantilla@tju.edu.cn

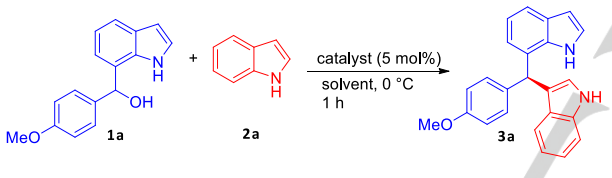
[b] We are grateful for financial support from the National 1000 Talent Plan of China, and for Tianjin University for start-up funds.

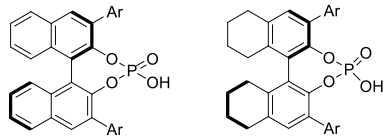
Supporting information for this article is given via a link at the end of the document.

arenes to *in situ* generated 6-methide-6*H*-indoles, providing a powerful and straightforward synthetic protocol for the hetero-triarylmethane derivatives. The challenging remote stereocontrol was successfully solved by the choice of a suitable chiral phosphoric acid (*R*)-**C2** and the rational design of 1,8-addition acceptor **9**. We reasoned that a CPA would not only promote the formation of the unstable 6-methide-6*H*-indoles from the racemic alcohols, but also simultaneously activate this intermediate by the more challenging propagation of the electronic effect through the conjugated system (LUMO lowering). The electron-rich indoles and *N*-protected indole **10** were chose as the nucleophiles to react with this active intermediate; resultantly a mono activation is suggestive. At this stage, the undesired electron-rich dienamine system might bring additional challenges for the reactivity (HOMO raising).

To test the feasibility of the 1,4-addition reaction, we chose the racemic alcohol **1a** as the electrophile, which could be easily converted to 7-methide-7H-indole through reaction with indole **2a** in the presence of a CPA catalyst. The initial catalyst screening (Table 1, entries 1-6) revealed that catalyst (*R*)-**A3** could efficiently promote this reaction and a moderate result (74% yield, 66% ee) was obtained. Additionally, a variety of different solvents (Table 1, entry 7) were explored, providing an inferior effect in terms of reaction efficiency and enantioselectivity. We found that by adding molecular sieves and lowering the temperature (Table 1, entries 8-11) significantly improved the enantiomeric excess and the isolated yield of the product, indicating that hydrogen bonding could play a crucial role in the stereocontrol.

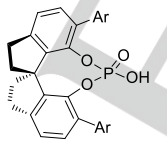
Table 1: Optimization of the 1,4-addition reaction conditions.[a]





A1: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$
A2: Ar = 9-anthracenyl
A3: Ar = 9-Phenanthrenyl

B1: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$

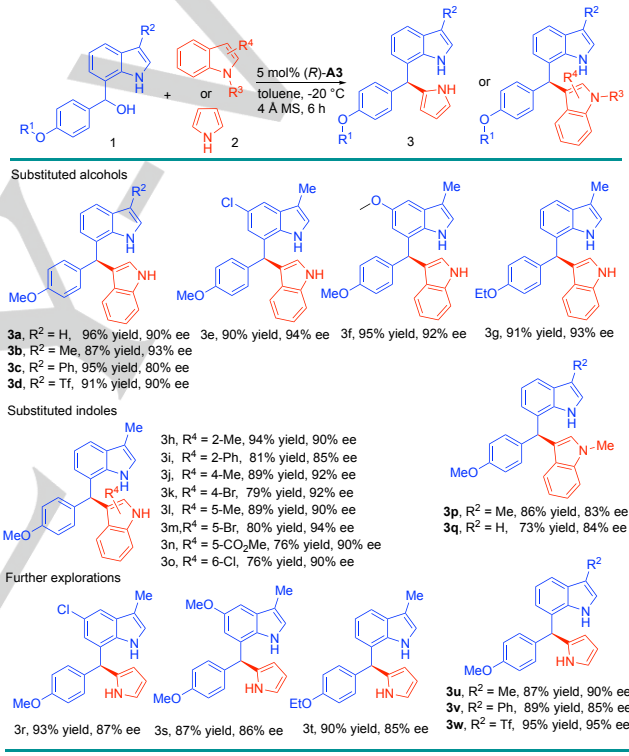


C1: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$
C2: Ar = 9-Phenanthrenyl

Entry	Catalyst	Solvent	Yield [%][b]	ee [%][c]
1	(*R*)-**A1**	toluene	72	47
2	(*R*)-**A2**	toluene	89	48
3	(*R*)-**A3**	toluene	74	66
4	(*R*)-**B1**	toluene	68	35
5	(*R*)-**C1**	toluene	53	60
6	(*R*)-**C2**	toluene	30	51
7	(*R*)-**A3**	CH_2Cl_2	64	41
8[d]	(*R*)-**A3**	toluene	77	78
9[d,e]	(*R*)-**A3**	toluene	83	86
10[d,f]	(*R*)-**A3**	toluene	96	90
11[d,g]	(*R*)-**A3**	toluene	75	91

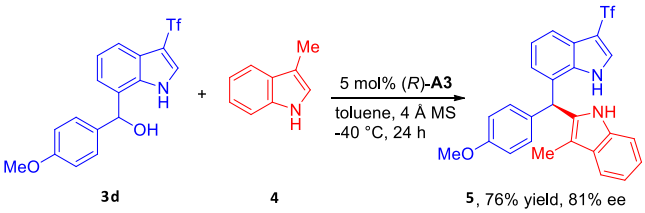
[a] Reactions were performed with **1a** (0.05 mmol), **2a** (0.075 mmol), and catalyst (5 mol%) in solvent (1.5 mL) at 0 °C. [b] Isolated yield. [c] The ee value was determined by HPLC analysis using a chiral stationary phase. [d] Run with 40 mg of 4 Å molecular sieves. [e] Run at -10 °C for 1h. [f] Run at -20 °C for 3h. [g] Run at -40 °C for 24h.

With the optimized conditions in hand, we investigated the substrate scope (Scheme 2) for the asymmetric 1,4-addition reaction. A series of racemic alcohols were efficient substrates, delivering the desired products **3a**-**3g** in 87-96% yield and 80-94% ee, respectively. Subsequently, we found the substrate scope **3h**-**3o** of indole was very broad. Presumably due to the steric hindrance around the reaction site, as well as the presence of electron-withdrawing groups, several products were obtained with slightly decreased yield. Importantly, 1-methylindole **2j** was also smoothly converted into the desired adducts **3p**-**3q** with good results, providing evidence for the mono activation mode. Surprisingly, this protocol was further extended to the less nucleophilic pyrrole series, and the corresponding adducts **3r**-**3w** were isolated in high yields with good to excellent enantioselectivities.



Scheme 2. Substrate scope of the 1,4-addition reaction.

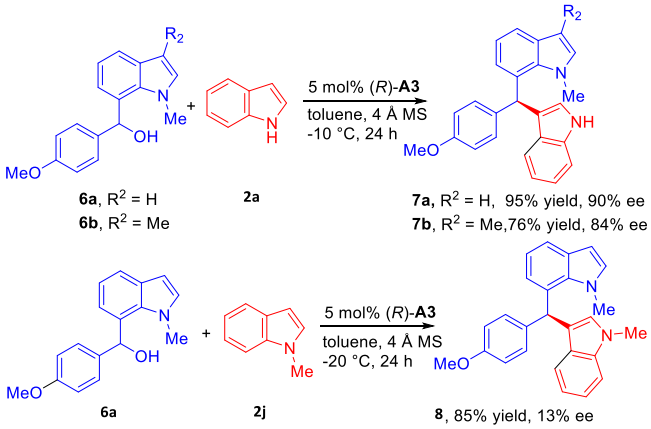
To further expand the utility of our process, we then investigated the possibility of C2-functionalization of a 3-substituted indole (Scheme 3). The alcohol **3d** bearing an electron-withdrawing group was employed as an electrophile to reduce competitive side reactions and the 3-methylindole **4** served as a nucleophile. To our delight, the corresponding product **5** was successfully obtained in 76% yield with 81% ee.



Scheme 3. Protocol for C2-functionalization of 3-substituted indoles

10.1002/anie.201804330

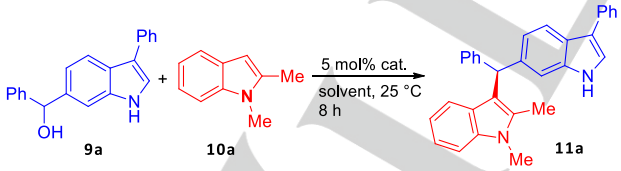
We then performed some control experiments to gain further insights into the possible mechanism (Scheme 4). Interestingly, the *N*-methyl protected diarylmethanols **6** could afford the desired products **7** in high yields and good ee's with longer reaction times, which suggested that a formal S_N1 substitution was also compatible with the same catalytic system. Additionally, the sharply decreased ee (13%) of product **8** provided experimental support for these two different activation modes. The absolute configuration of **7a**[16] was determined to be (*R*) by X-ray crystallographic analysis.



Scheme 4. The formal S_N1 substitutions and the mechanistic investigation for the 1,4-addition reaction

We successfully expanded the 1,4-addition reaction to a remote, yet enantioselective 1,8-addition reaction, by modifying the catalytic system and the substrate structure (from 7- to 6-indolylmethanol, in Table 2). This 1,8-addition reaction was conducted by employing the 6-indolylmethanol **9a** as an electrophile to react with the 1,2-dimethylindole **10a** in the presence of (*R*)-**A3**, with the desired product being obtained in 65% yield with 33% ee (Table 2, entry 1). The next investigation of various catalysts (Table 2, entries 2-4) showed that the SPINOL-derived phosphoric acid (*R*)-**C2** could give the best outcome. In addition, a variety of different solvents (Table 2, entries 5-7) were used to further examine the best conditions. It is found that benzene and its derivatives allowed for improved results. With the addition of 4 Å MS, a slight increase in terms of yield and ee was also observed (Table 2, entry 8).

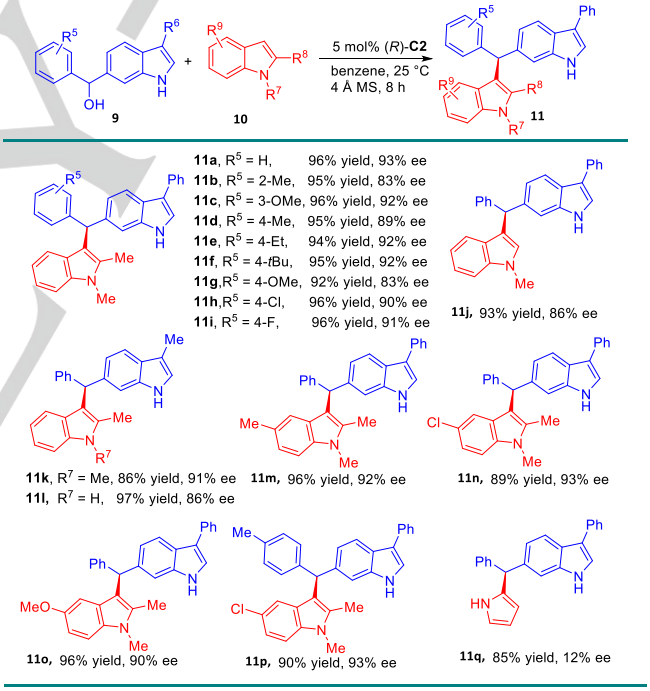
Table 2: Optimization of the 1,8-addition reaction conditions.[a]



Entry	Catalyst	Solvent	Yield [%][b]	ee [%][c]
1	(*R*)-**A3**	toluene	65	33
2	(*R*)-**B1**	toluene	83	18
3	(*R*)-**C1**	toluene	72	34
4	(*R*)-**C2**	toluene	81	78
5	(*R*)-**C2**	CH_2Cl_2	87	74
6	(*R*)-**C2**	CH_3CN	76	12
7	(*R*)-**C2**	benzene	89	84
8[d]	(*R*)-**C2**	benzene	96	93

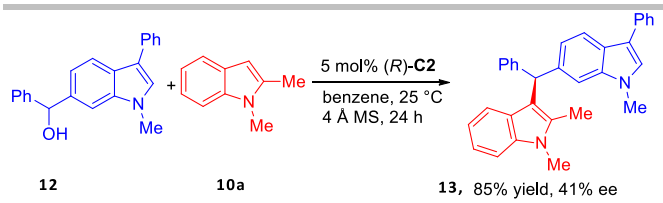
[a] Reactions were performed with **9a** (0.1 mmol), **10a** (0.15 mmol), and catalyst (5 mol%) in solvent (4 mL) at room temperature. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] Run with 40 mg 4 Å molecular sieves.

Having established the optimal reaction conditions, the scope of the asymmetric 1,8-addition reaction was subsequently explored (Scheme 5). Different substitution patterns on the phenyl ring **11a**-**11i**, regardless of its structural and electronic variations, were compatible with the catalytic system (92-96% yield, 83-93% ee). In the absence of the methyl group at the C2 position of 1,2-dimethylindole also proceeded well and produced the desired adduct **11j** with a slightly decreased ee. Importantly, the free NH bond in 2-methylindole **10c** had no obvious impact on the reaction outcome, providing **11i**. The results of reaction to give **11j** and **11i** showed that the steric hindrance on indole **10** contributed to the improved enantioselectivity. In addition, the exploration of substituted indoles **10d**-**10f** with different electronic properties showed a good tolerance and gave the similar results (**11m**-**11o**). It is worth noting that the less nucleophilic pyrrole also resulted in good reactivity, but low enantioselectivity.[15] Finally, the absolute configuration of **11p**[16] was determined to be (*S*) by X-ray crystallographic analysis.



Scheme 5. Substrate scope of 1,8-addition reaction.

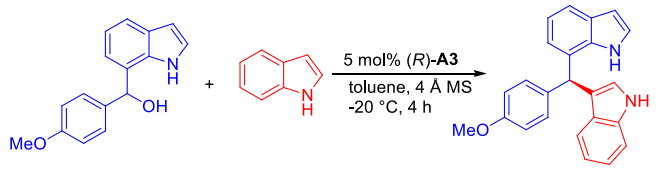
In order to gain a further understanding into the mechanism, we next conducted several control experiments (Scheme 6). The *N*-methylated substrate **12** allowed the corresponding product **13** to be formed with a decreased ee and longer reaction time. The methyl-protected alcohol **12** is not reactive, thus suggesting that successful formation of the 6-methide-6*H*-indoles intermediate is the key to the process.



12 10a 13, 85% yield, 41% ee

Scheme 6. The mechanistic investigation for the 1,8-addition reaction.

Finally, to further demonstrate the practicality of this remote strategy, the reaction of 7-indolylmethanl **1a** with indole **2a** was performed at one-gram scale with the standard conditions (Scheme 7). To our delight, the corresponding product **3a** was successfully obtained with slightly decreased yield and maintained enantioselectivity, which illustrates the practical application value of this enantioselective transformation.



1a, 1.0g **2a**, 532 mg **3a,** 1.1 g, 77%, 89% ee

Scheme 7. Gram-scale preparation of **3a**.

In conclusion, we have demonstrated the possibility to switch the reaction patterns and activation modes of designed diarylmethanols by means of CPA catalysis. The asymmetric transformation of 7-indolylmethanol features a broad substrate scope, low catalyst loading and flexible activation mode, providing an efficient and broadly applicable method for asymmetric synthesis of hetero-triarylmethanes. Moreover, the 1,4-addition reaction was further extended to include the remote 1,8-addition reaction with excellent yield and enantioselectivity. Control experiments provided important insights into the reaction mechanism. Interestingly, a mono-activation mode might be involved in this process, though not completely definitive without further experiments. Further expansion and application of diarylmethanols are currently under investigation in our laboratory and will be reported in due course.

Keywords: enantioselective catalysis•1,4-addition•1,8-addition •remote enantiocontrol•mono activation• chiral phosphoric acids

[1] a) M. Shiri, M. A. Zolfigol, H. G. Kruger, Z. Tanbakouchian, *Chem. Rev.***2010**, *110*, 2250; b) V. Nair, S. Thomas, S. C. Mathew, K. G. Abhilash, *Tetrahedron***2006**, *62*, 6731; c) H. V. Bossche, G. Willemsens, I. Roels, D. Bellens, H. Moereels, M. C. Coene, L. L. Jeune, W. Lauwers, P. A. J. Janssen, *Biochem. Pharmacol.***1990**, *40*, 1707; d) S. D. Cho, K. Yoon, S. Chintharlapalli, M. Abdelrahim, P. Lei, S. Hamilton, S. Khan, S. K. Ramaiah, S. Safe, *Cancer Res.***2007**, *67*, 674; e) X. Li, S. O. Lee, S. Stephen, *Biochem. Pharmacol.***2012**, *83*, 1445.

[2] For recent reviews on diarymethanols: a) N. J. Willis, C. D. Bray, *Chem. Eur. J.***2012**, *18*, 9160; b) Z. Wang, J. Sun, *Synthesis***2015**, *47*, 3629; c) A. Parra, M. Tortosa, *ChemCatChem***2015**, *7*, 1524; d) L. Caruana, M. Fochi, L. Bernardi, *Molecules***2015**, *20*, 11733; e) G. J. Mei, F. Shi, *J. Org. Chem.***2017**, *82*, 7695; f) P. Chauhan, U. Kaya, D. Enders, *Adv. Synth. Catal.* **2017**, *359*, 888.

[3] For some selected examples on the bi-functional mode: a) O. El-Sepelgy, S. Haseloff, S. K. Alamsetti, C. Schneider, *Angew. Chem. Int. Ed.***2014**, *53*, 7923; *Angew. Chem.***2014**, *126*, 8057; b) A. Chatupheeraphat, H. H. Liao, S. Mader, M. Sako, H. Sasai, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.***2016**, *55*, 4803; *Angew. Chem.***2016**, *128*, 4882; c) S. Saha, S. K. Alamsetti, C. Schneider, *Chem. Commun.***2015**, *51*, 1461; d) J. J. Zhao, S. B. Sun, S. H. He, Q. Wu, F. Shi, *Angew. Chem. Int. Ed.***2015**, *54*, 5460; *Angew. Chem.***2015**, *127*, 5550; e) B. Wu, Z. Yu, X. Gao, Y. Lan, Y. G. Zhou, *Angew. Chem. Int. Ed.***2017**, *56*, 4006; *Angew. Chem.***2017**, *129*, 4064.

[4] For some selected examples on the coordination catalysis: a) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Sun, *J. Am. Chem. Soc.***2015**, *137*, 383; b) W. Zhao, Z. Wang, B. Chu, J. Sun, *Angew. Chem. Int. Ed.***2015**, *54*, 1910; *Angew. Chem.***2015**, *127*, 1930; c) H. H. Liao, A. Chatupheeraphat, C. C. Hsiao, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.***2015**, *54*, 15540; *Angew. Chem.***2015**, *127*, 15760.

[5] For some selected examples on the dual ion-pairing type: a) Q. X. Guo, Y. G. Peng, J. W. Zhang, L. Song, Z. Feng, L. Z. Gong, *Org. Lett.***2009**, *11*, 4620; b) S. Qi, C. Y. Liu, J. Y. Ding, F. S. Han, *Chem. Commun.***2014**, *50*, 8605; c) Y. X. Gong, Q. Wu, H. H. Zhang, Q. N. Zhu, F. Shi, *Org. Biomol. Chem.***2015**, *13*, 7993.

[6] a) Y. C. Xiao, Q. Q. Zhou, L. Dong, T. Y. Liu, Y. C. Chen, *Org. Lett.* **2012**, *14*, 5940; b) K. Bera, C. Schneider, *Chem. Eur. J.* **2016**, *22*, 7074; c) K. Bera, C. Schneider, *Org. Lett.* **2016**, *18*, 5660.

[7] a) W. Tan, X. Li, Y. X. Gong, M. D. Ge, F. Shi, *Chem. Commun.* **2014**, *50*, 15901; b) C. Y. Liu, F. S. Han, *Chem. Commun.* **2015**, *51*, 11844; c) H. Zhang, C. Wang, C. Li, G. Mei, Y. Li, F. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 116; *Angew. Chem.* **2017**, *129*, 122.

[8] Similar effects were observed in reactions of quinone methides (QMs) or carbocationic species. a) L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2014**, *136*, 15929.

[9] a) W. D. Chu, L. F. Zhang, X. Bao, X. H. Zhao, C. Zeng, J. Y. Du, G. B. Zhang, F. X. Wang, X. Y. Ma, C. A. Fan, *Angew. Chem. Int. Ed.* **2013**, *52*, 9229; *Angew. Chem.* **2013**, *125*, 9399; b) L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2014**, *136*, 15929; c) M. Chen, J. Sun, *Angew. Chem. Int. Ed.* **2017**, *56*, 4583; *Angew. Chem.* **2017**, *129*, 4654; d) Z. Wang, Y. F. Wong, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 13711; *Angew. Chem.* **2015**, *127*, 13915; e) K. Zhao, Y. Zhi, A. Wang, D. Enders, *ACS Catal.* **2016**, *6*, 657; f) N. Dong, Z. P. Zhang, X. S. Xue, X. Li, J. P. Cheng, *Angew. Chem. Int. Ed.* **2016**, *55*, 1460; *Angew. Chem.* **2016**, *128*, 1482; g) S. Li, Y. Liu, B. Huang, T. Zhou, H. Tao, Y. Xiao, L. Liu, J. Zhang, *ACS Catal.* **2017**, *7*, 2805.

[10] For a review and examples of non-stereoselective 1,8-addition reactions, see: a) N. Krause, S. Thorand, *Inorg. Chim. Acta.* **1999**, *296*, 1; b) S. J. Brocchini, R. G. Lawton, *Tetrahedron Lett.* **1997**, *38*, 6319; c) S. C. George, S. Thulasi, S. Anas, K. V. Radhakrishnan, Y. Yamamoto, *Org. Lett.* **2011**, *13*, 4984.

[11] a) R. Mose, G. Preegel, J. Larsen, S. Jakobsen, E. H. Iversen,K. A. Jørgensen, *Nat. Chem.* **2017**, *9*, 487; b) Y. Hayashi, H. Gotoh, M. Honma, K. Sankar, I. Kumar, H. Ishikawa, K. Konno, H. Yui, S. Tsuzuki, T. Uchimaru, *J. Am. Chem. Soc.* **2011**, *133*, 20175; c) M. Xie, X. Liu, X. Wu, Y. Cai, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2013**, *52*, 5604; *Angew. Chem.* **2013**, *125*, 5714;

[12] a) D. Uraguchi, K. Yoshioka, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 19370; b) D. Qian, L. Wu, Z. Lin, J. Sun, *Nat. Comm.* **2017**, *8*, 567.

[13] a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; b) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890.

[14] a) T. Liang, Z. Zhang, J. C. Antilla, *Angew. Chem. Int. Ed.* **2010**, *49*, 9734; *Angew. Chem.* **2010**, *122*, 9928; b) G. L. Li, G. B. Rowland, E. B. Rowland, J. C. Antilla, *Org. Lett.* **2007**, *9*, 4065.

[15] However, the N-methyl protected pyrrole failed to afford the desired product.

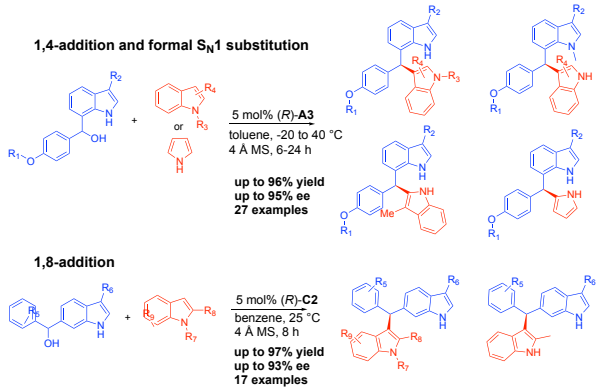
[16] CCDC 1835971 and 1835972 are contained in the supplementary material.

10.1002/anie.201804330

WILEY-VCH

Layout 2:

COMMUNICATION



Caizhen Yue, Fei Na, Xiantao Fang, Yang Cao and Jon C. Antilla*

Page No. – Page No.

Chiral phosphoric acid-catalyzed asymmetric synthesis of hetero-triarylmethanes from racemic indolyl alcohols

Remote activation protocols: The direct enantioselective 1,4- and 1,8-arylations of 7-methide-7*H*-indoles and 6-methide-6*H*-indoles, generated *in-situ* from diarylmethanols with electron-rich arenes as nucleophiles, has been achieved in the presence of chiral phosphoric acids. Mechanistically inspired experiments tentatively indicate that the formal S_N1 substitution is conceivable with this catalytic system. Interestingly, a mono-activation mode could be found in the 1,4- and the remote 1,8-addition process. A diversity of hetero-triarylmethanes with high yields was produced in excellent enantioselectivity.