ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue



Cite this: *Chem. Commun.*, 2013, **49**, 7750

Received 25th May 2013,
Accepted 2nd July 2013

DOI: 10.1039/c3cc43937b

www.rsc.org/chemcomm

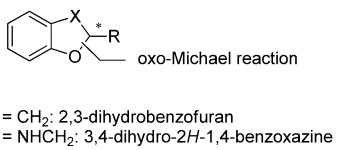
# Enantioselective synthesis of benzofurans and benzoxazines *via* an olefin cross-metathesis–intramolecular oxo-Michael reaction†

Jun-Wei Zhang,[ab] Quan Cai,[b] Qing Gu,[b] Xiao-Xin Shi[a] and Shu-Li You*[ab]

**Chiral phosphoric acid and Hoveyda–Grubbs II were found to catalyze an olefin cross-metathesis–intramolecular oxo-Michael cascade reaction of the *ortho*-allylphenols and enones to provide a variety of benzofuran and benzoxazine derivatives in moderate to good yields and enantioselectivity.**

2,3-Dihydrobenzofuran and 3,4-dihydro-2*H*-1,4-benzoxazine with a chiral center at the 2-position are common fragments in a number of biologically interesting compounds.[1] Asymmetric intramolecular oxo-Michael reaction[2] provides a facile construction of these chiral skeletons (Fig. 1). Although the first oxo-Michael reaction was reported in 1878,[3] surprisingly until recently highly enantioselective oxo-Michael reactions employing either chiral organocatalysts[4–6] or chiral Lewis acids[7] were not reported. It is mainly due to the intrinsic drawbacks of oxo-Michael reactions such as low reactivity and reversibility, which impede the development of highly enantioselective oxo-Michael reactions.

Recently, the concept of combining transition-metal catalysis and organocatalysis has emerged as a promising strategy for developing new transformations beyond the utilization of the single catalytic system.[8] In 2010, Fuwa *et al.*[9] reported a Hoveyda–Grubbs II catalyzed domino olefin cross-metathesis–intramolecular oxo-conjugate cyclization, affording a variety of substituted tetrahydropyrans from readily available starting materials. As part of our research program towards the development of enantioselective metal/organocatalyst sequential catalysis,[10] we envisaged that a sequential catalysis involving Ru-catalyzed cross-metathesis and chiral phosphoric acid-catalyzed asymmetric oxo-Michael reactions might be able to construct these chiral cyclic oxo containing skeletons.




X = $CH_2$: 2,3-dihydrobenzofuran
X = $NHCH_2$: 3,4-dihydro-2*H*-1,4-benzoxazine

**Fig. 1** Chiral benzofuran and benzoxazine derivatives.

We began our studies by examining several chiral Brønsted acids in combination with Hoveyda–Grubbs II in the tandem reaction of **1a** and **2a**. As summarized in Table 1, with 5 mol% chiral phosphoric acids **4** and 5 mol% Hoveyda–Grubbs II in $CH_2Cl_2$ at 40 °C, the reactions all proceeded smoothly to give the desired product in moderate to good yields and enantioselectivity.[11] Chiral phosphoric acid **4b** bearing triphenylsilyl groups proved to be an efficient catalyst, affording product **3a** in 56% yield with 78% ee (entry 2). When the corresponding stepwise reaction was attempted, we failed to obtain the intermediate **3a′** due to its facile cyclization during the purification. We also found a synergistic effect that the presence of chiral phosphoric acid could accelerate the overall reaction.[11]

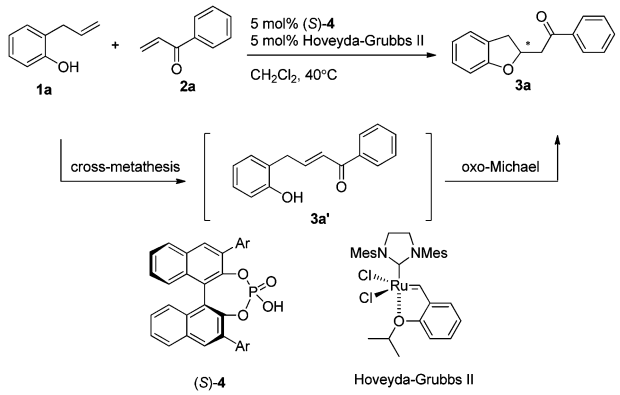
With 5 mol% (*S*)-**4b** and 5 mol% Hoveyda–Grubbs II as the catalyst, various solvents and other reaction parameters were further investigated. The results are summarized in Table 2. Various solvents such as $CHCl_3$, DCE, toluene and *o*-xylene all led to the formation of **3a** in comparable enantioselectivity but in decreased yields (entries 2–5). Ether could be used to afford product **3a** in 81% yield with a slightly decreased enantioselectivity (69% ee, entry 6). However, the reaction in THF or dioxane gave only a trace amount of desired product (entries 7 and 8). The addition of molecular sieves (entries 9 and 10) and change in the substrate concentration and reaction temperature did not give better results. The enantioselectivity is decreased with prolonged reaction time or high substrate concentration.

Under these optimized conditions [5 mol% (*S*)-**4b** in combination with 5 mol% Hoveyda–Grubbs II in $CH_2Cl_2$ at 40 °C], the substrate scope for the synthesis of 2,3-dihydrobenzofuran derivatives was investigated. The results are summarized in Table 3. Substituted phenols bearing an electron-donating

[a] *School of Pharmacy, East China University of Science and Technology, 130 Mei-Long Road, Shanghai 200237, China*
[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China. E-mail: slyou@sioc.ac.cn; Fax: +86 21-54925087*

† Electronic supplementary information (ESI) available: Experimental procedures and analysis data for new compounds, CIF files of **3m** and **7**. CCDC 937446 and 937447. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43937b

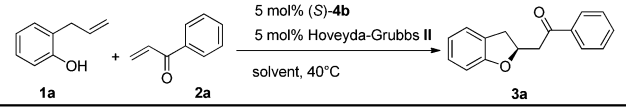
**Table 1** Screening of the chiral phosphoric acids[a]




| Entry | 4, Ar | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **4a**, 2,4,6-($^i$Pr)$_3$-C$_6$H$_2$ | 47 | 82 | 6 |
| 2 | **4b**, SiPh$_3$ | 48 | 56 | 78 |
| 3 | **4c**, 1-Naphthyl | 66 | 67 | −3 |
| 4 | **4d**, 9-Anthryl | 24 | 33 | −30 |
| 5 | **4e**, 9-Phenanthryl | 24 | 62 | −31 |
| 6 | **4f**, 2,6-($^i$Pr)$_2$-4-anthryl-C$_6$H$_2$ | 47 | 43 | 23 |
| 7 | **4g**, 3,5-(CF$_3$)$_2$-C$_6$H$_3$ | 45 | 39 | −19 |
| 8 | **4h**, 4-Biphenyl | 45 | 70 | −2 |
| 9 | **4i**, 4-(3′,5′-(CF$_3$)$_2$-C$_6$H$_3$)-C$_6$H$_4$ | 45 | 88 | 15 |
| 10 | **4j**, 4-NO$_2$-C$_6$H$_4$ | 45 | 90 | −13 |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.30 mmol), Hoveyda–Grubbs II (5 mol%) and chiral phosphoric acid (5 mol%) in $CH_2Cl_2$ (2 mL) at 40 °C. [b] Isolated yield. [c] Determined by HPLC.

**Table 2** Optimization of the reaction conditions for the tandem reaction[a]

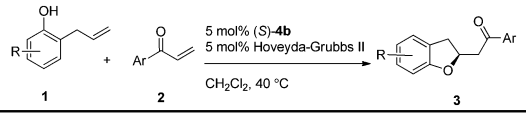



| Entry | Solvent | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | DCM | 48 | 56 | 78 |
| 2 | $CHCl_3$ | 67 | 14 | 75 |
| 3 | DCE | 88 | 21 | 69 |
| 4 | Toluene | 83 | 20 | 80 |
| 5 | *o*-Xylene | 88 | 21 | 82 |
| 6 | Ether | 96 | 81 | 69 |
| 7 | THF | 67 | 15 | 1 |
| 8 | Dioxane | 96 | Trace | nd |
| 9[d] | DCM | 5 | 63 | 75 |
| 10[e] | DCM | 15 | 54 | 75 |

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), Hoveyda–Grubbs II (5 mol%) and (*S*)-**4b** (5 mol%) in solvent (2 mL, $c$ = 0.1 mol L$^{-1}$ for **1a**) at 40 °C. [b] Isolated yield. [c] Determined by HPLC. [d] 4 Å MS (100 mg) was added. [e] 5 Å MS (100 mg) was added.

group (4-Me, 4-$^i$Pr, 4-$^t$Bu, 4-Ph, 4-OMe, 5-OMe and 6-OMe, entries 2–8) or an electron-withdrawing group (4-Br, entry 9) were well tolerated, and their corresponding cross-metathesis and oxo-Michael adducts were obtained in good yields (40–72%) and enantioselectivity (66–80% ee). The *ortho* substituted phenol (6-OMe) could also be tolerated but with slightly decreased enantioselectivity (66% ee, entry 8). In addition, the reaction is also general for the enones bearing different aromatic groups. The enones containing either an electron-donating group (4-Me, 4-OMe) or an electron-withdrawing group (4-Cl, 4-Br) on the phenyl ring all led to the formation of the desired products in

**Table 3** Scope of the enantioselective oxo-Michael reaction for the synthesis of benzofurans[a]



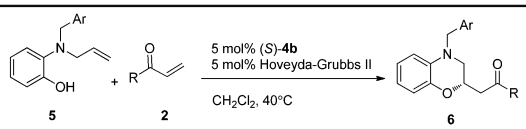

| Entry | 3: R, Ar | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **3a**: H, C$_6$H$_5$ | 48 | 56 | 78 |
| 2 | **3b**: 4-Me, C$_6$H$_5$ | 12 | 49 | 79 |
| 3 | **3c**: 4-$^i$Pr, C$_6$H$_5$ | 12 | 72 | 78 |
| 4 | **3d**: 4-$^t$Bu, C$_6$H$_5$ | 23 | 64 | 76 |
| 5 | **3e**: 4-Ph, C$_6$H$_5$ | 12 | 53 | 76 |
| 6 | **3f**: 4-OMe, C$_6$H$_5$ | 12 | 52 | 74 |
| 7 | **3g**: 5-OMe, C$_6$H$_5$ | 24 | 46 | 80 |
| 8 | **3h**: 6-OMe, C$_6$H$_5$ | 12 | 59 | 66 |
| 9 | **3i**: 4-Br, C$_6$H$_5$ | 24 | 40 | 79 |
| 10 | **3j**: H, 4-MeC$_6$H$_4$ | 12 | 49 | 81 |
| 11 | **3k**: H, 4-MeOC$_6$H$_4$ | 12 | 38 | 76 |
| 12 | **3l**: H, 4-ClC$_6$H$_4$ | 12 | 51 | 79 |
| 13 | **3m**: H, 4-BrC$_6$H$_4$ | 12 | 61 | 77 |
| 14 | **3n**: H, 4-NO$_2$C$_6$H$_4$ | 12 | 75 | 50 |
| 15 | **3o**: H, 2-naphthyl | 12 | 49 | 79 |

[a] Reaction conditions as in entry 1, Table 2. [b] Isolated yield. [c] Determined by HPLC.

good yields and enantioselectivity (entries 10–13). 2-Naphthyl enone could also be tolerated to afford **3o** in 49% yield and 79% ee (entry 15). However, *para*-nitro substituted enone gave the product in 50% ee (entry 14). The absolute configuration of the product was determined by an X-ray crystallographic analysis of the single crystal of enantiopure **3m** as (*S*).

In addition to allyl phenols that afforded chiral 2,3-dihydrobenzofuran derivatives, the 2-*N*-allyl substituted phenols were also examined to yield chiral oxazine derivatives. The results are summarized in Table 4. When the *N*-benzyl allyl substituted phenol was used, various aromatic enones could react smoothly under the optimized conditions affording the desired products in 44–65% yields and 67–77% ee (Table 4, entries 1–8). It is

**Table 4** Scope of the enantioselective oxo-Michael reaction for the synthesis of benzoxazines[a]




| Entry | 6: R, Ar | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **6a**: C$_6$H$_5$, C$_6$H$_5$ | 24 | 65 | 77 |
| 2 | **6b**: 4-MeC$_6$H$_4$, C$_6$H$_5$ | 10 | 54 | 74 |
| 3 | **6c**: 4-MeOC$_6$H$_4$, C$_6$H$_5$ | 24 | 64 | 67 |
| 4 | **6d**: 2-BrC$_6$H$_4$, C$_6$H$_5$ | 11 | 44 | 69 |
| 5 | **6e**: 4-BrC$_6$H$_4$, C$_6$H$_5$ | 11 | 52 | 76 |
| 6 | **6f**: 4-ClC$_6$H$_4$, C$_6$H$_5$ | 8 | 48 | 73 |
| 7 | **6g**: 4-NO$_2$C$_6$H$_4$, C$_6$H$_5$ | 5 | 52 | 75 |
| 8 | **6h**: 2-naphthyl, C$_6$H$_5$ | 12 | 51 | 76 |
| 9 | **6i**: Me, C$_6$H$_5$ | 5 | 76 | 76 |
| 10 | **6j**: Et, C$_6$H$_5$ | 12 | 81 | 78 |
| 11 | **6k**: $^n$Pr, C$_6$H$_5$ | 12 | 67 | 82 |
| 12 | **6l**: Me, 1-naphthyl | 12 | 58 | 79 |
| 13 | **6m**: Me, 2-naphthyl | 14 | 63 | 64 |

[a] Reaction conditions as in entry 1, Table 2. [b] Isolated yield. [c] Determined by HPLC.

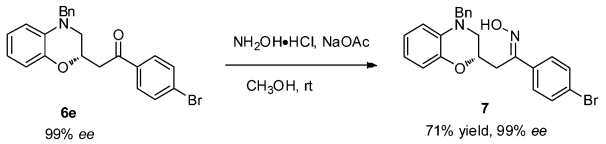



**Fig. 2** Synthesis of oxime **7**.



worth noting that both aliphatic enones (entries 9–11) and naphthyl protected phenols (entries 12 and 13) were suitable substrates (58–81% yields, 64–82% ee).

The chiral oxazine derivatives **6e** (99% ee from recrystallization) could be easily transformed into oxime **7** in 71% yield without the loss of enantiomeric purity (Fig. 2). The absolute configuration of the product was determined by an X-ray crystallographic analysis of the single crystal of enantiopure oxime derivative **7** as (*S*).

In conclusion, we have developed a chiral phosphoric acid in combination with a Hoveyda–Grubbs II catalyzed olefin cross-metathesis–asymmetric oxo-Michael reaction, affording a variety of benzofuran and benzoxazine derivatives in moderate to good yields and enantioselectivity.

We thank the National Basic Research Program of China (973 Program 2010CB833300) and the NSFC (21025209, 21002111, 21121062) for generous financial support.

## Notes and references

1 (*a*) D. M. Bowen, J. I. DeGraw Jr, V. R. Shah and W. A. Bonner, *J. Med. Chem.*, 1963, **6**, 315; (*b*) A. H. Banskota, Y. Tezuka, J. K. Prasain, K. Matsushige, I. Saiki and S. Kadota, *J. Nat. Prod.*, 1998, **61**, 896; (*c*) C. L. Céspedes, A. Uchoa, J. R. Salazar, F. Perich and F. Pardo, *J. Agric. Food Chem.*, 2002, **50**, 2283; (*d*) M. Sefkow, *Synthesis*, 2003, 2595; (*e*) F. Touzeau, A. Arrault, G. Guillaumet, E. Scalbert, B. Pfeiffer, M.-C. Rettori, P. Renard and J.-Y. Mérour, *J. Med. Chem.*, 2003, **46**, 1962; (*f*) B. Achari, S. B. Mandal, P. K. Dutta and C. Chowdhury, *Synlett*, 2004, 2449; (*g*) J. Ilaš, P. Š. Anderluh, M. S. Dolenc and D. Kikelj, *Tetrahedron*, 2005, **61**, 7325; (*h*) G.-H. Chu, M. Gu, J. A. Cassel, S. Belanger, T. M. Graczyk, R. N. DeHaven, N. Conway-James, M. Koblish, P. J. Little, D. L. DeHaven-Hudkins and R. E. Dolle, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5114; (*i*) J. L. Cohen, A. Limon, R. Miledi and A. R. Chamberlin, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2189; (*j*) J. Duan, L. Wang, S. Qian, S. Su and Y. Tang, *Arch. Pharmacal Res.*, 2008, **31**, 965; (*k*) S. K. Dinda, S. K. Das and G. Panda, *Synthesis*, 2009, 1886; (*l*) Z. Liu and Y. Chen, *Tetrahedron Lett.*, 2009, **50**, 3790.

2 For reviews: (*a*) C. F. Nising and S. Bräse, *Chem. Soc. Rev.*, 2008, **37**, 1218; (*b*) C. F. Nising and S. Bräse, *Chem. Soc. Rev.*, 2012, **41**, 988.

3 F. Loydl, *Justus Liebigs Ann. Chem.*, 1878, **192**, 80.

4 Secondary amine catalysis: (*a*) T. Govender, L. Hojabri, F. M. Moghaddam and P. I. Arvidsson, *Tetrahedron: Asymmetry*, 2006, **17**, 1763; (*b*) T. Kano, Y. Tanaka and K. Maruoka, *Tetrahedron*, 2007, **63**, 8658; (*c*) H. Sundén, I. Ibrahem, G.-L. Zhao, L. Eriksson and A. Córdova, *Chem.–Eur. J.*, 2007, **13**, 574; (*d*) S. Bertelsen, P. Dinér, R. L. Johansen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 1536; (*e*) D.-Q. Xu, Y.-F. Wang, S.-P. Luo, S. Zhang, A.-G. Zhong, H. Chen and Z.-Y. Xu, *Adv. Synth. Catal.*, 2008, **350**, 2610; (*f*) H. Li, J. Wang, T. E-Nunu, L. Zu, W. Jiang, S. Wei and W. Wang, *Chem. Commun.*, 2007, 507; (*g*) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.*, 2009, **11**, 1627; (*h*) E. Reyes, G. Talavera, J. L. Vicario, D. Badía and L. Carrillo, *Angew. Chem., Int. Ed.*, 2009, **48**, 5701; (*i*) P. Kotame, B.-C. Hong and J.-H. Liao, *Tetrahedron Lett.*, 2009, **50**, 704; (*j*) X. Zhang, S. Zhang and W. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 1481; (*k*) C. Liu, X. Zhang, R. Wang and W. Wang, *Org. Lett.*, 2010, **12**, 4948; (*l*) J. Alemán, A. Núñez, L. Marzo, V. Marcos, C. Alvarado and J. L. G. Ruano, *Chem.–Eur. J.*, 2010, **16**, 9453.

5 Thiourea and alkaloid catalysis: (*a*) E. Sekino, T. Kumamoto, T. Tanaka, T. Ikeda and T. Ishikawa, *J. Org. Chem.*, 2004, **69**, 2760; (*b*) A. Merschaert, P. Delbeke, D. Daloze and G. Dive, *Tetrahedron Lett.*, 2004, **45**, 4697; (*c*) C. Dittmer, G. Raabe and L. Hintermann, *Eur. J. Org. Chem.*, 2007, 5886; (*d*) M. M. Biddle, M. Lin and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 3830; (*e*) N. Saito, A. Ryoda, W. Nakanishi, T. Kumamoto and T. Ishikawa, *Eur. J. Org. Chem.*, 2008, 2759; (*f*) F.-G. Zhang, Q.-Q. Yang, J. Xuan, H.-H. Lu, S.-W. Duan, J.-R. Chen and W.-J. Xiao, *Org. Lett.*, 2010, **12**, 5636; (*g*) T. Okamura, K. Asano and S. Matsubara, *Chem. Commun.*, 2012, **48**, 5076; (*h*) K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2012, **134**, 16711.

6 Chiral Brønsted acid catalysis: (*a*) Q. Gu, Z.-Q. Rong and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 4056; (*b*) I. Čorić, S. Vellalath and B. List, *J. Am. Chem. Soc.*, 2010, **132**, 8536; (*c*) I. Čorić, S. Müller and B. List, *J. Am. Chem. Soc.*, 2010, **132**, 17370; (*d*) V. Rauniyar, A. D. Lackner, G. L. Hamilton and F. D. Toste, *Science*, 2011, **334**, 1681; (*e*) D. M. Rubush, M. A. Morges, B. J. Rose, D. H. Thamm and T. Rovis, *J. Am. Chem. Soc.*, 2012, **134**, 13554; (*f*) Z. Sun, G. A. Winschel, A. Borovika and P. Nagorny, *J. Am. Chem. Soc.*, 2012, **134**, 8074; (*g*) I. Čorić and B. List, *Nature*, 2012, **483**, 315.

7 Chiral Lewis acid catalysis: (*a*) C. D. Vanderwal and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 14724; (*b*) L. Wang, X. Liu, Z. Dong, X. Fu and X. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 8670.

8 For reviews on the combination of transition metal and chiral phosphoric acid: (*a*) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2009, **38**, 2745; (*b*) M. Rueping, R. M. Koenigs and I. Atodiresei, *Chem.–Eur. J.*, 2010, **16**, 9350; (*c*) J. Zhou, *Chem.–Asian J.*, 2010, **5**, 422; (*d*) C. Zhong and X. Shi, *Eur. J. Org. Chem.*, 2010, 2999; (*e*) Z. Du and Z. Shao, *Chem. Soc. Rev.*, 2013, **42**, 1337.

9 H. Fuwa, K. Noto and M. Sasaki, *Org. Lett.*, 2010, **12**, 1636.

10 (*a*) Q. Cai, Z.-A. Zhao and S.-L. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 7428; (*b*) Q. Cai, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2010, **49**, 8666; (*c*) Q. Cai, X.-W. Liang, S.-G. Wang, J.-W. Zhang, X. Zhang and S.-L. You, *Org. Lett.*, 2012, **14**, 5022; (*d*) Q. Cai, X.-W. Liang, S.-G. Wang and S.-L. You, *Org. Biomol. Chem.*, 2013, **11**, 1602.

11 For detailed information, see ESI†.