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Organocatalytic enantioselective aza-Friedel–Crafts reaction of 2-naphthols with benzoxathiazine 2,2-dioxides†

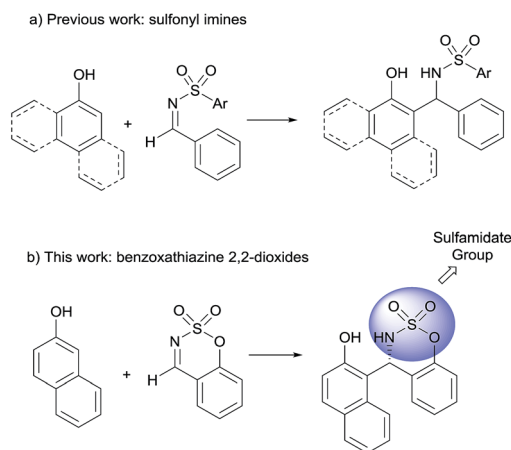
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An organocatalytic enantioselective aza-Friedel–Crafts addition of 2-naphthols to benzoxathiazine 2,2-dioxides is described using a quinine-derived bifunctional catalyst. The method allows the use of a wide range of aromatic compounds as nucleophiles, including 1-naphthol and sesamol, and benzoxathiazines 2,2-dioxides, expanding the existing state of the art enantioselective synthesis of aminomethylnaphthol derivatives.

The enantioselective addition of aromatic compounds to imines (aza-Friedel–Crafts reaction) is an important strategy for the synthesis of enantioenriched benzylic amines, which are present in a wide variety of natural products.¹ The addition of indoles to different imines has been, by far, the most studied example, especially using chiral phosphoric acids derived from BINOL as a catalyst.² However, the enantioselective addition of arenes with lower nucleophilicity has been less developed. Enders presented the phosphoric acid catalyzed addition of activated arenes to imino esters in 2010, obtaining excellent results in terms of enantioselectivity, although it suffered from long reaction times.³ Moreover, Hui reported in 2010 the addition of 2-naphthols to tosyl aldimines using a stoichiometric amount of a dinuclear zinc–aminoalcohol complex, obtaining the desired product with good results.^{4a} The first substoichiometric versions of this reaction were published in 2011 almost simultaneously by Wang and Chimni. Both authors employed Cinchona alkaloid derivatives to catalyze the addition of 1-naphthols or 2-naphthols, respectively, to sulfonylimines.^{4b,c} Both groups found Cinchona alkaloids bearing a hydroxyl group in the C6' position were ideal catalysts for this transformation and proposed a transition state where

nucleophile and electrophile are simultaneously activated. More recently, two examples of 2-naphthol addition to tosyl aldimines have been reported using a vanadium complex as metal catalyst^{4d} or a chiral trisimidazoline as organocatalyst.^{4e} All these examples used sulfonyl imines as electrophiles and the scope regarding to naphthols was certainly narrow (Scheme 1a).

On the other hand, benzoxathiazine 2,2-dioxides have recently emerged as interesting substrates in several enantioselective transformations. The benzoxathiazine 2,2-dioxides are a special kind of cyclic imines, derived from salicylic aldehydes, which have a rigid structure that reduces their conformational mobility and avoid the *E/Z* isomerization, facilitating the stereo differentiation and making them optimum partners for enantioselective transformations. Additionally, the sulfamate moiety generated after the addition reaction is a versatile functional group which is present in biologically active compounds (Fig. 1).⁵ Consequently, benzoxathiazine 2,2-dioxides have been used in several transition metal catalyzed enantioselective transformations such as hydrogenation,



Scheme 1 Enantioselective aza-Friedel–Crafts reactions of naphthols with imines.

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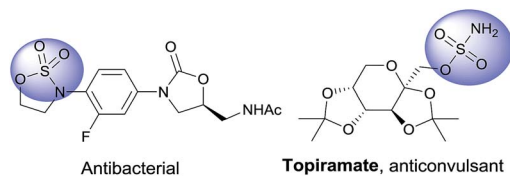


Fig. 1 Biologically active sulfamidates.

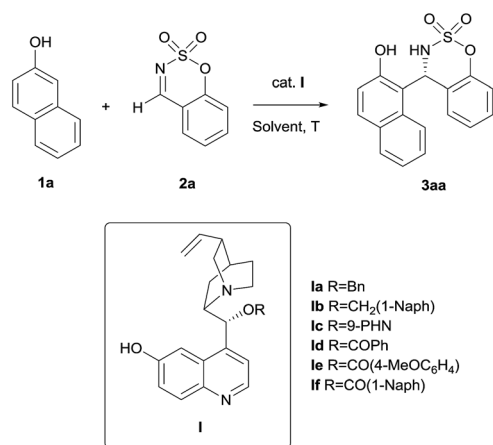
alkenylation, allylation, arylation, Mannich reactions and alkylation.⁶ They have also been used in organocatalyzed reactions, such as Diels–Alder reaction with α,β -unsaturated imines, Mannich reaction with acetone, [4 + 2] cycloadditions with enones and ynones or [4 + 2] cycloaddition with allenates.⁷ Although arylations of related imines with aryl boronic derivatives have been described,^{6e–gj} the enantioselective Friedel–

Crafts addition of nucleophilic arenes to benzoxathiazine 2,2-dioxides has not been reported yet.

We envisioned that the organocatalytic asymmetric aza-Friedel–Crafts reaction of naphthols to benzoxathiazine 2,2-dioxides could be carried out, expanding the applicability of the Friedel–Crafts reaction and accessing to a new family of enantioenriched aminomethylnaphthols, which are of great interest in medicinal chemistry and as chiral ligands.⁸

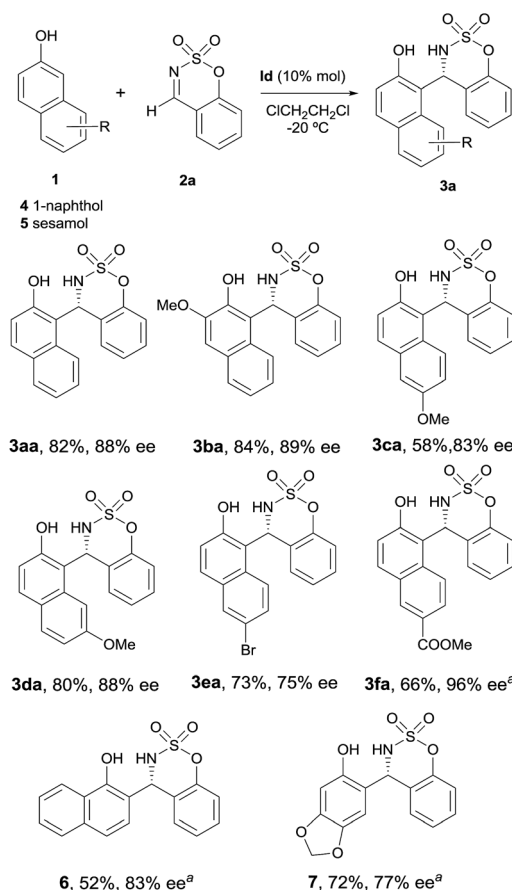
We started our study screening different bifunctional catalysts in the addition of 2-naphthol (**1a**) to benzoxathiazine 2,2-dioxide (**2a**) and we found that 9-O-benzylcupreine (**1a**) (which derives from quinine) met optimal structural characteristics for this transformation,^{9,10} confirming that the free 6'-OH moiety was key for an optimum enantioselectivity.¹¹ Next, we examined different solvents and temperatures, obtaining our best results using chlorinated solvents, specially 1,2-dichloroethane and performing the reaction at $-20\text{ }^{\circ}\text{C}$ (Table 1, entry 6). Then, we tested different cupreine derivatives with varied substituents on the secondary hydroxyl group. We observed that the presence of a bulkier benzylic substituent, as in catalyst **1b**, had no effect on the enantioselectivity (Table 1,

Table 1 Optimization of enantioselective aza-Friedel–Crafts reaction of 2-naphthol (**1a**) and benzoxathiazine 2,2-dioxide (**2a**)^a



Entry	Catalyst	Solvent	T (°C)	t (h)	Yield ^b (%)	ee ^c (%)
1	1a	CH ₂ Cl ₂	0	44	90	52
2	1a	Toluene	0	16	82	22
3	1a	THF	25	48	<10	—
4	1a	CHCl ₃	0	24	99	50
5	1a	ClCH ₂ CH ₂ Cl	0	24	88	65
6	1a	ClCH ₂ CH ₂ Cl	-20	24	84	80
7	1a	ClCH ₂ CH ₂ Cl	-30	48	78	75
8	1a	ClCH ₂ CH ₂ Cl	-10	20	74	72
9	1b	ClCH ₂ CH ₂ Cl	-20	24	72	79
10	1c	ClCH ₂ CH ₂ Cl	-20	24	78	70
11	1d	ClCH ₂ CH ₂ Cl	-20	24	88	86
12	1e	ClCH ₂ CH ₂ Cl	-20	24	75	83
13	1f	ClCH ₂ CH ₂ Cl	-20	24	81	81
14 ^d	1d	ClCH ₂ CH ₂ Cl	-20	36	82	88
15 ^e	1d	ClCH ₂ CH ₂ Cl	-20	36	80	88

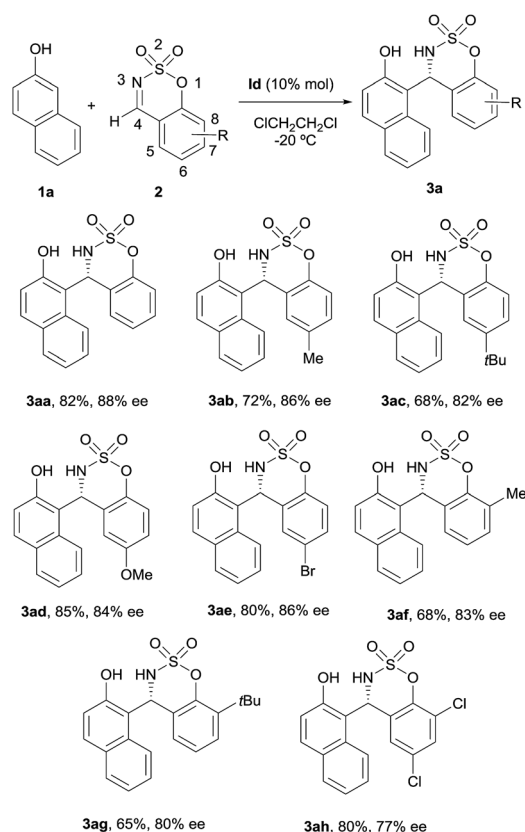
^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (20% mol) and solvent (1.0 mL). ^b Isolated yield. ^c Determined by chiral HPLC analysis. ^d Naphthol was added dissolved in 0.5 mL of ClCH₂CH₂Cl to a solution of imine and catalyst (10% mol) in 0.5 mL of ClCH₂CH₂Cl during 12 h using a syringe pump. ^e Imine was added to a solution of naphthol and catalyst.



Scheme 2 Scope of the aza-Friedel–Crafts reaction of benzoxathiazine 2,2-dioxide (**2a**) with different arenes (**1**, **4**, **5**). Reaction conditions: to a solution of **1** (0.1 mmol) and catalyst **1d** (0.01 mmol) in ClCH₂CH₂Cl at $-20\text{ }^{\circ}\text{C}$, **2a** (0.1 mmol) was added using a syringe pump, reaction time: 36 h. ^aReaction carried out at $0\text{ }^{\circ}\text{C}$ during 72 h, without syringe pump.

entry 9) whilst catalyst **1c** with a bulky aromatic group (PHN = phenanthryl) directly linked to the oxygen was less efficient (Table 1, entry 10). Finally, we checked different acyl substituents on the secondary hydroxyl group, obtaining the best result with the benzoyl derivative **1d** (Table 1, entry 11). A reduction of the catalyst loading had a detrimental effect on the enantiomeric excess. However, to our delight we were able to overcome this drawback by adding the nucleophile dissolved in 1,2-dichloroethane slowly to a solution of the benzoxathiazine 2,2-dioxide and the catalyst using a syringe pump. This new procedure allowed us to decrease the amount of catalyst to 10% mol, providing the product **3aa** with 82% yield and 88% ee (Table 1, entry 14). Interestingly, the slow addition of the imine **2a** to a solution of naphthol **1a** and catalyst **1d** provided comparable results, in terms of yield and enantioselectivity (Table 1, entry 15).

With the optimized reaction conditions in hand, we studied the scope of the reaction regarding to the nucleophile employing 2-naphthols with electron-donating groups in different positions (Scheme 2). The desired sulfamidates **3** were isolated in good to high yields and excellent enantioselectivities. The reaction is also compatible with electron-withdrawing groups such as bromide or an ester group. Remarkably, when 6-methoxycarbonyl-2-naphthol was used as the nucleophile,



Scheme 3 Scope of the aza-Friedel-Crafts reaction of 2-naphthol (**1a**) with different benzoxathiazine 2,2-dioxides (**2**). Reaction conditions: to a solution of **2** (0.1 mmol) and catalyst **Id** (0.01 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ at -20°C , **1a** (0.1 mmol) was added using a syringe pump, reaction time: 36 h.

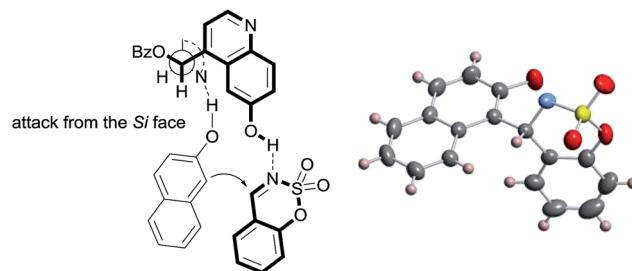
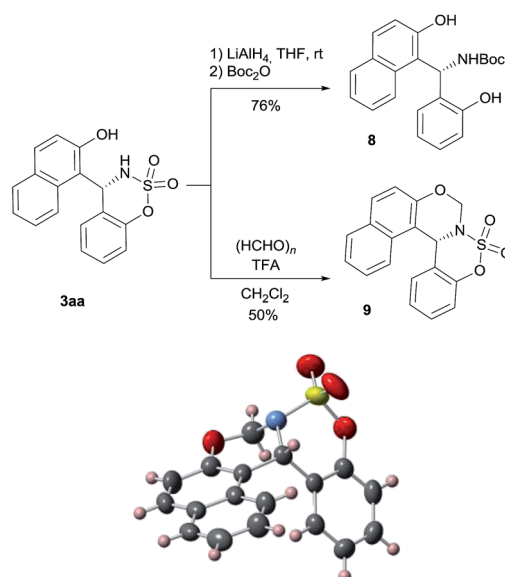


Fig. 2 Proposed transition state and X-ray structure of compound **3aa**.

product **3fa** was obtained with 96% ee. Finally, we demonstrated the wide applicability of our method, reacting imine **2a** with 1-naphthol (**4**) and sesamol (**5**), obtaining the corresponding products, **6** and **7** respectively, in moderate to good yields and good enantiomeric excesses. The aminomethylsesamol moiety, or its derivatives, is present in molecules with antitumor or antibacterial properties, such as oxazapodophyllotoxin **1**,¹² and some methods have been recently described for the enantioselective addition of this electron-rich phenol to tosyl imines.¹³

Next, we applied the optimized conditions to different benzoxathiazine 2,2-dioxides (Scheme 3). Both electron-donating and electron-withdrawing groups with different steric demand in the 6-position were well tolerated. This methodology was also suitable for the addition of 2-naphthol to imines bearing alkyl groups in the 8-position of the benzoxathiazine 2,2-dioxide and also for the disubstituted derivative **2h**.

Product **3aa** was recrystallized from hexanes/ethyl acetate in order to obtain enantiopure crystals. The X-ray analysis of these revealed an *R* absolute stereochemistry, as a result of the attack of the naphthol to the *Si* face of the benzoxathiazine 2,2-dioxide.



Scheme 4 Synthetic transformations of **3aa** and X-ray structure of compound **9**.

For the rest of the products a uniform reaction mechanism was assumed (see ESI† for further details). The observed stereochemistry can be explained through a transition state involving a tertiary complex between the catalyst and the substrates.^{4c} The hydrogen bonding between the quinuclidine tertiary amine and the naphthol OH group explains also the absence of reaction of 2-methoxynaphthalene under the optimised reaction conditions (Fig. 2).

Finally, we carried out some synthetic transformations on the product **3aa**. The reduction of the sulfamidate group using LiAlH₄ yielded the corresponding aminomethylphenol, which was protected as its Boc derivative **8** in a one pot procedure, in high yield and without loss of optical purity. Additionally, pentacyclic compound **9** was prepared after acidic treatment of product **3aa** in the presence of paraformaldehyde. We were able to obtain a crystal of this product which was suitable for X-ray diffraction,¹⁴ confirming the absolute configuration obtained for product **3aa** (Scheme 4).

Conclusions

In summary, we present an organocatalytic enantioselective aza-Friedel–Crafts reaction employing naphthols (and a electron-rich phenol) and benzoxathiazine 2,2-dioxides as reaction partners and 9-*O*-benzoylated cupreine (**Id**) as bifunctional catalyst. The corresponding chiral sulfamidates were obtained in good yields and enantioselectivities, which can be interesting products from both synthetic and medicinal chemistry points of view. This method represents the first enantioselective Friedel–Crafts addition of electron-rich arenes to benzoxathiazine 2,2-dioxides.

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Notes and references

- (a) T. C. Nugent, *Chiral Amine Synthesis: Methods, Developments and Applications*, Wiley-VCH, Weinheim, 2010; (b) G. A. Olah, *Friedel–Crafts Chemistry*, Wiley, New York, 1973; (c) M. Bandini and A. Umani-Ronchi, *Catalytic Asymmetric Friedel–Crafts Alkylations*, Wiley-VCH, Weinheim, 2009; (d) S. Kobayashi, Y. Mori, J. S. Fossey and M. M. Salter, *Chem. Rev.*, 2011, **111**, 2626–2704; (e) G. K. Mathies and A. K. Frestad, *Tetrahedron*, 2007, **63**, 2541–2569.
- For Lewis acid catalyzed reactions: (a) M. Johannsen, *Chem. Commun.*, 1999, 2233–2234; (b) S. Saaby, X. Fang, N. Gathergood and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2000, **39**, 4114–4116; (c) Y.-X. Jia, J.-H. Xie, H.-F. Duan, L.-X. Wang and Q.-L. Zhou, *Org. Lett.*, 2006, **8**, 1621–1624; (d) B. L. Wang, N. K. Li, J. X. Zhang, G. G. Liu, T. Liu, Q. Shen and X. W. Wang, *Org. Biomol. Chem.*, 2011, **9**, 2614–2617, for chiral phosphoric acid catalyzed reactions; (e) M. Terada and K. Sorimachi, *J. Am. Chem. Soc.*, 2007, **129**, 292–293; (f) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2007, **46**, 5565–5567; (g) Q. Kang, Z.-A. Zhao and S.-L. You, *J. Am. Chem. Soc.*, 2007, **129**, 1484–1485; (h) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman and J. C. Antilla, *Org. Lett.*, 2007, **9**, 4065–4068; (i) M. Terada, S. Yokoyama, K. Sorimachi and D. Uruguchi, *Adv. Synth. Catal.*, 2007, **349**, 1863–1867; (j) G.-W. Zhang, L. Wang, J. Nie and J.-A. Ma, *Adv. Synth. Catal.*, 2008, **350**, 1457–1463; (k) Q. Kang, X.-J. Zheng and S.-L. You, *Chem.–Eur. J.*, 2008, **14**, 3539–3542; (l) M. Rueping, S. Raja and A. Nuñez, *Adv. Synth. Catal.*, 2011, **353**, 563–568; (m) J. Feng, W. Yan, D. Wang, P. Li, Q. Sun and R. Wang, *Chem. Commun.*, 2012, **48**, 8003–8005; (n) R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping and C. Bolm, *Org. Lett.*, 2011, **13**, 1044–1047; (o) K.-F. Zhang, J. Nie, R. Guo, Y. Zheng and J.-A. Ma, *Adv. Synth. Catal.*, 2013, **355**, 3497–3502; (p) M. Rueping and B. J. Nachtsheim, *Synlett*, 2010, 119–122; (q) K. Wu, M.-H. Zhuo, D. Sha, Y.-S. Fan, D. An, Y.-J. Jiang and S. Zhang, *Chem. Commun.*, 2015, 8054–8057, for organocatalysts other than CPA; (r) Y.-Q. Wang, J. Song, R. Hong, H. Li and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 8156–8157; (s) P. Yu, J. He and C. Guo, *Chem. Commun.*, 2008, 2355–2357; (t) E. A. Peterson and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2009, **48**, 6328–6331; (u) Y. Quian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao and V. H. Rawal, *Chem. Commun.*, 2010, 3004–3006.
- D. Enders, M. Seppelt and T. Beck, *Adv. Synth. Catal.*, 2010, **352**, 1413–1418.
- (a) L.-F. Niu, Y.-C. Xin, R.-L. Wang, F. Jiang, P.-F. Xu and X.-P. Hui, *Synlett*, 2010, 765–768; (b) G. Liu, S. Zhang, H. Li, T. Zhang and W. Wang, *Org. Lett.*, 2011, **13**, 828–831; (c) P. Chauhan and S. S. Chimni, *Eur. J. Org. Chem.*, 2011, 1636–1640; (d) S. Takizawa, F. A. Arteaga, Y. Yoshida, J. Kadera, Y. Nagata and H. Sasai, *Dalton Trans.*, 2013, 11787–11790; (e) S. Takizawa, S. Hirata, K. Murai, H. Fujiokab and H. Sasai, *Org. Biomol. Chem.*, 2014, **12**, 5827–5830; (f) Very recently, our group has reported the enantioselective addition of naphthols and electron-rich phenols to isatin-derived ketimines; M. Montesinos-Magraner, C. Vila, R. Cantón, G. Blay, I. Fernández, M. C. Muñoz and J. R. Pedro, *Angew. Chem., Int. Ed.*, 2015, **54**, 6320–6324.
- (a) P. M. When and J. Du Bois, *Org. Lett.*, 2005, **7**, 4685–4688; (b) J. F. Bower, J. Rujirawanicha and T. Gallagher, *Org. Biomol. Chem.*, 2010, **8**, 1505–1519; (c) S. J. Kim, M.-H. Jung, K. H. Yoo, J.-H. Cho and C.-H. Oh, *Bioorg. Med. Chem. Lett.*, 2008, 5815–5818; (d) S. J. Kim, H. B. Park, J. S. Lee, N. H. Jo, K. H. Yoo, D. Baek, B.-W. Kang, J.-H. Cho and C.-H. Oh, *Eur. J. Med. Chem.*, 2007, 1176–1183; (e) S. R. Hanson, L. J. Whalen and C.-H. Wong, *Bioorg. Med. Chem.*, 2006, 8386–8395.

- 6 (a) Y.-Q. Wang, C.-B. Yu, D.-W. Wang, X.-B. Wang and Y.-G. Zhou, *Org. Lett.*, 2008, **10**, 2071–2074. Alkenylation; (b) Y. Luo, A. J. Carnell and H.-W. Lam, *Angew. Chem., Int. Ed.*, 2012, **51**, 6762–6766, allylations; (c) Y. Luo, H.-B. Hepburn, N. Chotsaeng and H.-W. Lam, *Angew. Chem., Int. Ed.*, 2012, **51**, 8309–8313; (d) H. B. Hepburn, N. Chotsaeng, Y. Luo and H.-W. Lam, *Synthesis*, 2013, 2649–2661, arylations; (e) H. Wang, T. Jiang and M.-H. Xu, *J. Am. Chem. Soc.*, 2013, **135**, 971–974; (f) C. Jiang, Y. Lu and T. Hayashi, *Angew. Chem., Int. Ed.*, 2014, **53**, 9936–9939; (g) M.-H. Xu and H. Wang, *Synthesis*, 2013, 2125–2133, Mannich; (h) H.-X. Zhang, J. Nie, H. Cai and J.-A. Ma, *Org. Lett.*, 2014, **16**, 2542–2545, alkynylation; (i) L. De Munck, A. Monleón, C. Vila, M. C. Muñoz, J. R. Pedro, *Org. Biomol. Chem.*, 2015, **13**, 7393–7396, for arylation reaction with ketimines; (j) T. Jiang, Z. Wang and M.-H. Xu, *Org. Lett.*, 2015, **17**, 528–531.
- 7 (a) C. Ma, J. Gu, B. Teng, Q.-Q. Zhou, R. Li and Y.-C. Chen, *Org. Lett.*, 2013, **15**, 6206–6209; (b) Y. Liu, T.-R. Kang, Q.-Z. Liu, L.-M. Chen, Y.-C. Wang, J. Liu, Y.-M. Xie, J.-L. Yang and L. He, *Org. Lett.*, 2013, **15**, 6090–6093; (c) Y.-Q. Wang, X.-Y. Cui, Y.-Y. Ren and Y. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 9101–9104; (d) H. Yu, L. Zhang, Z. Li, H. Liu, B. Wang, Y. Xiao and H. Guo, *Tetrahedron*, 2014, **70**, 340–348.
- 8 (a) I. Szatmari, T. A. Martinek, L. Lazar and F. Fülöp, *Eur. J. Org. Chem.*, 2004, 2231–2238; (b) D.-X. Liu, L.-C. Zhang, Q. Wang, C.-S. Da, Z.-Q. Xin, R. Wang, M. C. K. Choi and A. S. C. Chan, *Org. Lett.*, 2001, **3**, 2733–2735; (c) C. Cimarrelli, G. Palmieri and E. Volpini, *Tetrahedron: Asymmetry*, 2002, **13**, 2417–2426; (d) J.-X. Ji, L.-Q. Qiu, C. W. Yip and A. S. C. Chan, *J. Org. Chem.*, 2003, **68**, 1589–1590; (e) Y. Dong, J. Sun, X. Wang, X. Xu, L. Cao and Y. Hu, *Tetrahedron: Asymmetry*, 2004, **15**, 1667–1672; (f) X. Wang, Y. Dong, J. Sun, X. Xu, R. Li and Y. Hu, *J. Org. Chem.*, 2005, **70**, 1897–1900.
- 9 More detailed data described in the ESI.†
- 10 (a) H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906–9907; (b) X. Liu, H. Li and L. Deng, *Org. Lett.*, 2005, **7**, 167–169; (c) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman and L. Deng, *Angew. Chem., Int. Ed.*, 2005, **44**, 105–108; (d) H. Li, B. Wang and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 732–773; (e) Y. Wang, X. Liu and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 3928–3930; (f) T. Mandal, S. Samanta and C.-G. Zhao, *Org. Lett.*, 2007, **9**, 943–945; (g) M. Bandini, R. Sinisi and A. Umani-Ronchi, *Chem. Commun.*, 2008, 4360–4362.
- 11 P. Chauhan and S. S. Chimni, *RSC Adv.*, 2012, **2**, 737–758.
- 12 (a) Y. Hitotsuyanagi, Y. Ichihara, K. Takeya and H. Itokawa, *Tetrahedron Lett.*, 1994, **35**, 9401–9402; (b) L. Jurd, *J. Heterocycl. Chem.*, 1985, **22**, 993–995.
- 13 (a) S. Bai, Y. Liao, L. Lin, W. Luo, X. Liu and X. Feng, *J. Org. Chem.*, 2014, **79**, 10662–10668; (b) P. Chauhan and S. S. Chimni, *Tetrahedron Lett.*, 2013, **54**, 4613–4616. For other enantioselective aza-Friedel–Crafts addition with an electron-rich phenol: G.-X. Li and J. Qu, *Chem. Commun.*, 2012, **48**, 5518–5520.
- 14 See ESI.†