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Enantioselective Reaction between 2-(Cyanomethyl)azaarenes and *N*-Boc-amino Sulfones

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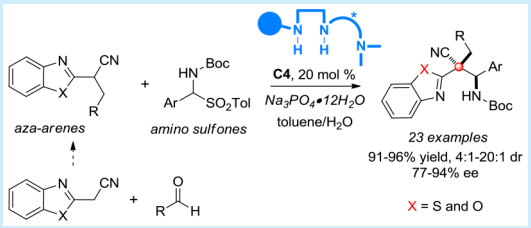
Supporting Information

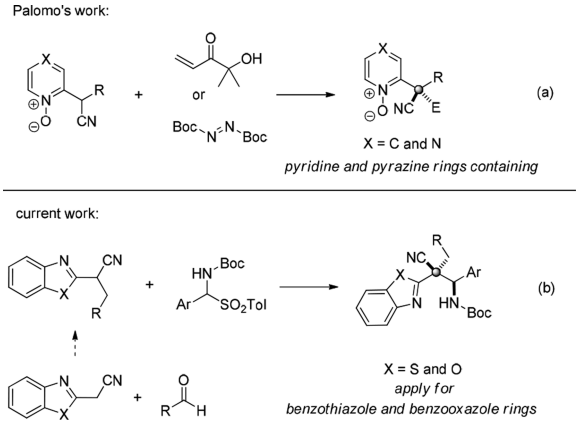
ABSTRACT: A series of 2-(cyanomethyl)azaarenes containing benzothiazole or benzoxazole were designed and synthesized for asymmetric α-functionalization with *N*-Boc-amino sulfones. The Mannich adducts were obtained in high yields with good diastereo- and enantioselectivities. Aryl-substituted amino sulfones were tolerated under the current conditions, and the reaction can be performed on gram scale in good results.



Nitrogen-containing aromatic heterocycles (azaarenes) are important building motifs in chiral biological pharmaceuticals and agrochemicals. Thus, it would be highly valuable to construct adjacent stereocenters in enantioenriched compounds containing azaarenes. Compared with the well-established asymmetric Friedel−Crafts reactions for building chiral azaarene skeletons, especially with enamine-containing azaarenes such as indoles or pyrroles,[1] the catalytic enantioselective reactions employing substrates containing azaarene-embedded imine structures are relatively less developed.[2] To date, there are representative methods to accomplish these chiral compounds; these reactions can be divided into two classes: one is catalytic asymmetric reactions on the basis of functions on alkenylazaarenes, including reduction, boration, or additions;[3−5] the other is 2-alkylazaarenes toward nucleophilic additions or allylic alkylations under catalytic asymmetric systems.[6,7] In this context, by analyzing the established documented methods, it is observed that there are still limited studies on constructing α-quaternary stereocenters in building imine-embedded azaarene-containing systems. In 2016, Palomo and co-workers reported an excellent asymmetric carbo- and hetero-α-functionalization of 2-cyanomethylazaarene *N*-oxides; pyridine and pyrazine were utilized in this mild and direct system (Scheme 1, a).[8] Here, we design and synthesize benzothiazole- or benzoxazole-containing nucleophiles and apply them in the asymmetric α-functionalization with *N*-carbamoyl imines generated in situ (Scheme 1, b).[9]

Initial experiments studied the reaction between benzothiazolyl nuclephile **1a** and amino sulfone **2a** catalyzed by a series of well-developed bifunctional hydrogen-bond catalysts (Table 1; see the Supporting Information (SI) for detailed screening

Scheme 1. Alkylazaarenes in Construction of α-Quaternary Stereocenters



progress). In the initial screening process, **C3** was selected for studying the effects of different bases (Table 1, entries 3−12, and SI). It was observed that bases influence the reaction obviously, and $Na_3PO_4·12H_2O$ showed relatively better results. Further selection processes identified **C4** as the optimal catalyst,[10] leading to the desired addition product **3a** in satisfactory results (Table 1, entry 13).

Having the optimal conditions in hand, next we explored the generality of amino sulfones. As the results illustrate in Table 2, various aryl- amino sulfones, including mono- or polysubstituted aryl rings with different electron properties, reacted

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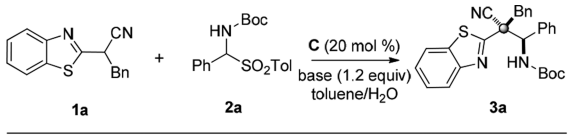
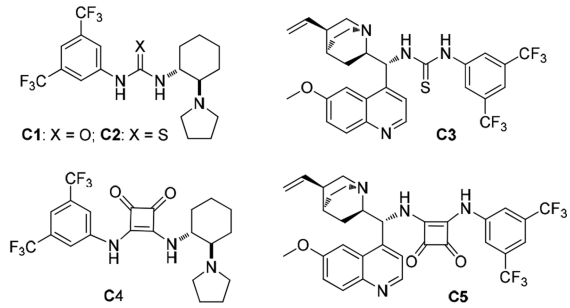
Table 1. Optimization Process of the Reaction[a]





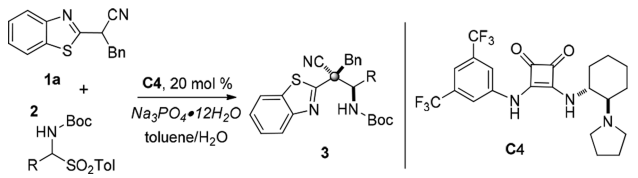
entry	C	base	yield[b] (%)	dr[c]	ee[d] (%)
1	**C1**	K_2CO_3	96	3:1	35
2	**C2**	K_2CO_3	97	3:1	38
3	**C3**	K_2CO_3	94	7:1	63
4	**C3**	$KF{\cdot}2H_2O$	93	6:1	57
5	**C3**	$LiOH{\cdot}H_2O$	95	3.5:1	39
6	**C3**	Na_2CO_3	92	15:1	61
7	**C3**	Li_2CO_3			
8	**C3**	CH_3COONa	94	8:1	51
9	**C3**	CH_3COOK	93	15:1	63
10	**C3**	$K_3PO_4{\cdot}3H_2O$	95	15:1	65
11	**C3**	$Na_3PO_4{\cdot}12H_2O$	96	15:1	68
12	**C3**	Na_2HPO_4	88	2:1	<10
13	**C4**	$Na_3PO_4{\cdot}12H_2O$	96	9:1	94
14	**C5**	$Na_3PO_4{\cdot}12H_2O$	93	8:1	89
15[e]	**C4**	$Na_3PO_4{\cdot}12H_2O$	90	3:1	61
16[f]	**C4**	$Na_3PO_4{\cdot}12H_2O$	88	4:1	85
17[g]	**C4**	$Na_3PO_4{\cdot}12H_2O$	89	3:1	47
18[h]	**C4**	$Na_3PO_4{\cdot}12H_2O$	<10		

[a]Reactions were carried out with **1a** (0.10 mmol), **2a** (0.12 mmol), catalysts (0.02 mmol, 20 mol %), and bases (0.12 mmol) in toluene (0.8 mL) and H_2O (0.2 mL) at room temperature for 48 h. [b]Isolated yields were reported. [c]The dr were determined by ^1H NMR analysis. [d]Analyzed by chiral HPLC. [e]In hexane. [f]In DCM. [g]In Et_2O. [h]Carried out at 0 °C.

with heterocyclic arenes under direct and mild conditions, leading to the desired chiral benzothiazolyl amino products in excellent yields with moderate to good selectivities. However, the current conditions were not suitable to alkylamino sulfones; only trace amounts of product could be detected under the bifunctional catalytic system (Table 2, entry 14), and the related direct reaction with prepared *N*-Boc-imines also failed with some of the substrates. Moreover, the absolute configuration of the adduct was determined by X-ray crystallographic analysis of **3c**.

Furthermore, different aza-arene containing nucleophiles were synthesized and introduced into the reaction conditions with amino sulfone **2a** (Scheme 2). A series of alkyl-substituted benzothiazolyl nucleophiles were obtained and applied in the Mannich reaction, and the desired addition amines were obtained smoothly with good yields and enantioselectivities. Moreover, a benzoxazolyl-substituted substrate was also synthesized with similar methods and carried out under the optimal conditions, leading to the corresponding adduct **3v** in 91% yield, 15:1 dr, and 86% ee values. Notably, the 4-

Table 2. Substrate Scope with Respect to *N*-Boc-amino Sulfones[a]



entry	R	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**	96	9:1	94
2	**3b**	93	20:1	94
3	**3c**	96	15:1	82
4	**3d**	91	6:1	78
5	**3e**	95	4:1	80
6	**3f**	88	6:1	77
7	**3g**	92	8:1	92
8	**3h**	92	10:1	85
9	**3i**	94	7:1	88
10	**3j**	93	13:1	93
11	**3k**	91	12:1	78
12	**3l**	94	6:1	83
13	**3m**	92	4:1	80
14		<5	-	-

[a]Reactions were carried out with **1a** (0.10 mmol), **2** (0.12 mmol), **C4** (0.02 mmol, 20 mol %), and $Na_3PO_4{\cdot}12H_2O$ (0.12 mmol) in toluene (0.8 mL) and H_2O (0.2 mL) at room temperature for 48 h. [b]Isolated yields were reported. [c]The dr were determined by ^1H NMR analysis. [d]Analyzed by chiral HPLC.

methylthiazolyl nucleophile was also compatible with the current method and generated the Mannich adduct **3w** in 90% yield with 89% ee (Scheme 2).

However, frankly, some azaarene substrates failed to generate the desired Mannich adducts under the current conditions; the examples we tried are listed in Scheme 3, including pyridinyl, aryl-substituted thiazolyl, and benzoimidazolyl nucleophiles, which were not compatible and only led to a trace amount of the addition products even at 60 °C.

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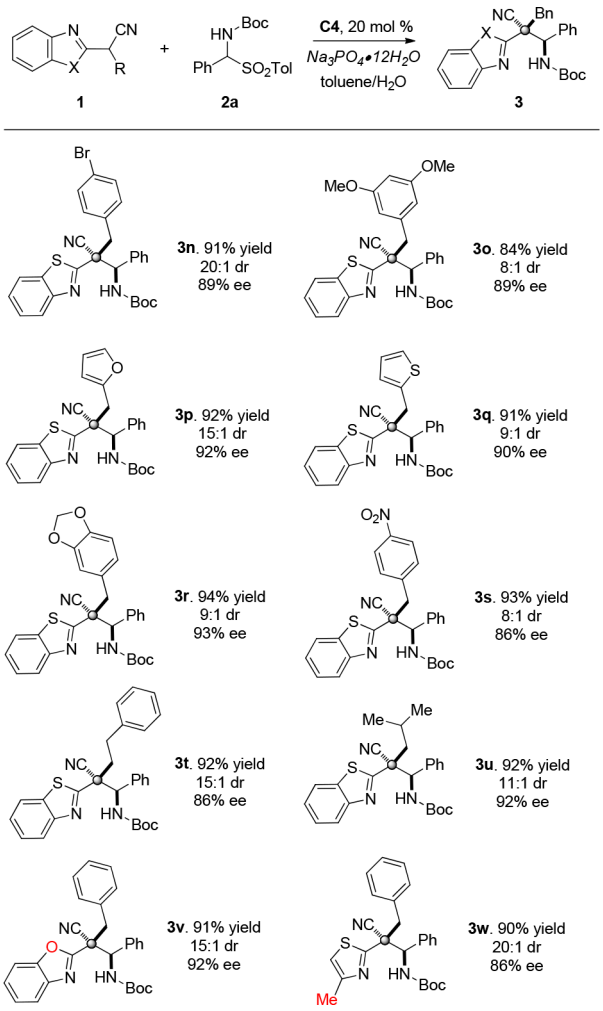
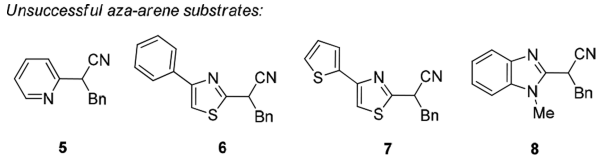
Scheme 2. Substrates Scope with Respect to Azaarenes



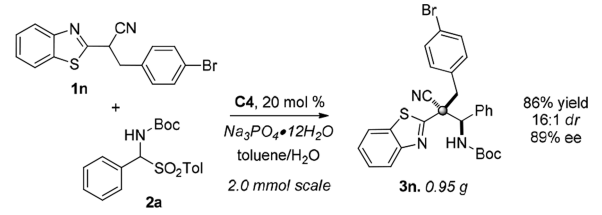
Scheme 3. Unsuccessful Azaarene Nucleophiles of the Reaction Conditions



Finally, the current method was performed on gram scale and led to the adduct in similar results under optimal conditions, as expected (Scheme 4, **3n**, 86% yield, 16:1 dr, 89% ee).

In summary, we have synthesized a series of novel 2-cyanomethylazaarenes and applied them in catalytic asymmetric Mannich reactions. The reaction can be performed directly with amino sulfones under mild conditions in the presence of a well-developed bifunctional hydrogen-bond catalyst. Aryl-substituted imine precursors are good substrates with optimal conditions, and benzothiazole and benzoxazole are well tolerated azaarenes in the designed nucleophiles. There are still limitations of the current methods with regard to substrate scope, and further work investigating different catalytic strategies to more broad scope with respect to imines and azaarenes is underway in our laboratory.

Scheme 4. Gram-Scale Synthesis of the Current Method



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02205.

Experimental procedures, characterization of all compounds, and detailed information on our mechanistic studies (PDF)

Accession Codes

CCDC 1856394 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For examples of reviews, see: (a) You, S. L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (b) Zeng, M.; You, S. L. *Synlett* **2010**, *2010*, 1289. (c) Terrasson, V.; Marcia de Figueiredo, R.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, *2010*, 2635. (d) Chauhan, P.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 6117.

(2) For a recent review, see: Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831.

(3) (a) Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386. (b) Jung, H.-Y.; Feng, X.; Kim, H.; Yun, J. *Tetrahedron* **2012**, *68*, 3444. (c) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746. (d) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10830.

(4) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934.

(5) (a) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373. (b) Kobayashi, T.; Yorimitsu, H.; Oshima, K. *Chem.* -

DOI: 10.1021/acs.orglett.8b02205
Org. Lett. XXXX, XXX, XXX−XXX

Asian J. **2011**, *6*, 669. (c) Friedman, A. A.; Panteleev, J.; Tsoung, J.; Huynh, V.; Lautens, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9755.
(6) (a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (b) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056. (c) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 12439. (d) Jiang, X.; Boehm, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2018**, *140*, 1239.
(7) (a) Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193. (b) Fallan, C.; Lam, H. W. *Chem. - Eur. J.* **2012**, *18*, 11214. (c) Li, T.; Zhu, J.; Wu, D.; Li, X.; Wang, S.; Li, H.; Li, J.; Wang, W. *Chem. - Eur. J.* **2013**, *19*, 9147. (d) Bastida, I.; Segundo, M. S.; López, R.; Palomo, C. *Chem. - Eur. J.* **2017**, *23*, 13332.
(8) Izquierdo, J.; Landa, A.; Bastida, I.; López, R.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2016**, *138*, 3282.
(9) For reviews on amino sulfones, see: (a) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949. (b) Monleón, A. *Synlett* **2013**, *24*, 529 For recent examples, see:. (c) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975. (d) Song, J.; Shih, H. W.; Deng, L. *Org. Lett.* **2007**, *9*, 603. (e) Zhang, H.; Syed, S.; Barbas, C. F., III *Org. Lett.* **2010**, *12*, 708. (f) Zhao, D.; Yang, D.; Wang, Y.; Wang, Y.; Wang, L.; Mao, L.; Wang, R. *Chem. Sci.* **2011**, *2*, 1918. (g) Wang, Q.; Leutzsch, M.; van Gemmeren, M.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 15334.
(10) For examples on squaramide as the catalyst, see: (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (b) Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 16050. (c) Blümel, M.; Chauhan, P.; Hahn, R.; Raabe, G.; Enders, D. *Org. Lett.* **2014**, *16*, 6012. (d) Bera, K.; Namboothiri, I. N. N. *J. Org. Chem.* **2015**, *80*, 1402. (e) Wang, M. H.; Cohen, D. T.; Schwamb, C. B.; Mishra, R. K.; Scheidt, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 5891. (f) Işık, M.; Unver, M. Y.; Tanyeli, C. *J. Org. Chem.* **2015**, *80*, 828. (g) Zhu, Y.; Li, X.; Chen, Q.; Su, J.; Jia, F.; Qiu, S.; Ma, M.; Sun, Q.; Yan, W.; Wang, K.; Wang, R. *Org. Lett.* **2015**, *17*, 3826. (h) Zhao, B.-L.; Du, D.-M. *Org. Lett.* **2017**, *19*, 1036. (i) Zhao, B.-L.; Du, D.-M. *Org. Lett.* **2018**, *20*, 3797.

DOI: 10.1021/acs.orglett.8b02205
Org. Lett. XXXX, XXX, XXX−XXX