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COMMUNICATION

Synthesis of (1*R*,2*R*)-DPEN-derived triazolium salts and their application in asymmetric intramolecular Stetter reactions†

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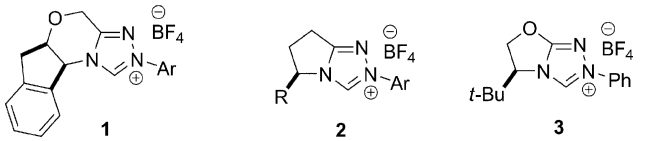
A series of novel chiral triazolium salts has been synthesized from readily available (1*R*,2*R*)-DPEN and found to be efficient for the enantioselective intramolecular Stetter reaction. With 10 mol% of the catalyst, the intramolecular Stetter reaction was realized in excellent yields with up to 97% ee.

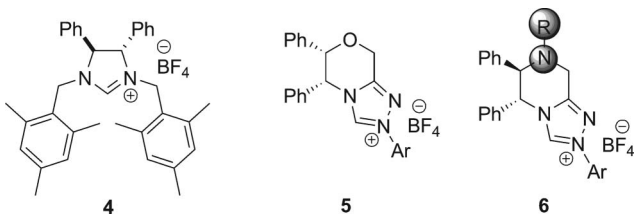
N-Heterocyclic carbenes (NHCs) as organocatalysts have received considerable attention in the last two decades.[1–2] Various kinds of chiral NHCs have been developed to catalyze asymmetric reactions, in which the bicyclic triazolium salts **1–3** are one of the highly efficient classes (Scheme 1). Their bicyclic molecular scaffolds can restrict unfavorable internal rotation around the N–C (substituent) axis, which may enhance the chiral induction. Moreover, the aryl groups on the nitrogen atom may affect both reactivity and selectivity. Because of their structural advantages, these triazolium salts have achieved great success in many asymmetric reactions.[3–5]



Scheme 1 Chiral bicyclic triazolium salts.

However, there exist only a limited number of backbone scaffolds for chiral NHCs, and most of them suffer from high cost of the enantiopure starting materials and tedious synthetic procedures. The development of a novel NHC catalyst that can be synthesized from a readily available chiral source and is fine-tunable with steric and electronic properties is highly desirable.

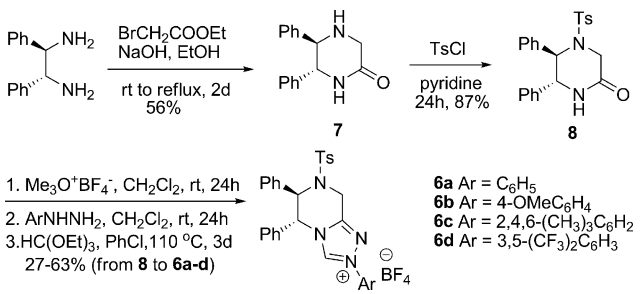
(1*R*,2*R*)-DPEN ((1*R*,2*R*)-(+)-diphenyl ethylenediamine) has been used widely as an excellent chiral source for chiral auxiliary and organic synthesis.[6] Tomioka *et al.* reported the synthesis of dihydroimidazolium salt **4** in 2006, and applied it as organocatalyst in the intramolecular asymmetric Stetter reaction with up to 80% ee.[7] In 2007, Scheidt and co-workers devised bicyclic triazolium salts **5** derived from the (1*S*,2*R*)-(+)-2-amino-1,2-diphenyl ethanol backbone and found they were highly efficient in desymmetrization of 1,3-diketones (up to 96% ee)[8] and addition of homoenolates to nitrones (up to 94% ee).[9] We therefore envisaged that (1*R*,2*R*)-DPEN might be an efficient chiral scaffold for triazolium salts, precursors for NHC catalysts. Compared with the bicyclic triazolium salts **5** derived from (1*S*,2*R*)-(+)-2-amino-1, 2-diphenyl ethanol backbone, bicyclic triazolium salts **6** based on (1*R*,2*R*)-DPEN scaffold show the advantage of having fine-tunable R group (Scheme 2).



Scheme 2 Several related *N*-heterocyclic carbene precursors.

As part of our ongoing endeavors to develop new *N*-heterocyclic carbene catalysts and their applications to novel organocatalytic reactions,[10] in this paper, we report our preliminary results on the synthesis of novel chiral bicyclic triazolium salts from (1*R*,2*R*)-DPEN and their application to the asymmetric catalytic intramolecular Stetter reaction.

A series of triazolium salts were easily prepared from the commercially available (1*R*,2*R*)-DPEN[11] (Scheme 3). With these catalyst precursors in hand, we then examine their catalytic ability in the intramolecular Stetter reaction.



Scheme 3 Synthesis of triazolium salts from (1*R*,2*R*)-DPEN.

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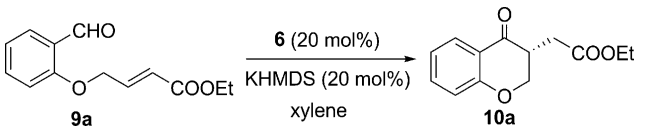
Our studies began with testing different chiral NHCs in the intramolecular Stetter reaction of **9a**. As summarized in Table 1, when triazolium salts **6a–6d** (20 mol%) were used together with KHDMS (20 mol%), generally appreciable enantioselectivities in the cyclization were afforded (entries 1–4, Table 1). NHC derived from triazolium salt **6c** led to the Stetter reaction product **10a** in excellent yield and promising asymmetric induction (95% yield and 85% ee, entry 3, Table 1). With **6c**, the catalyst loading could be decreased to 10 mol% without significantly affecting the reactivity and only slight erosion of the ee value was observed (entry 5, Table 1). Several conventional bases were found tolerable (entries 1–5, Table 2) and Et_3N was optimal in terms of both yield and ee of the product (entry 6, Table 2). Various solvents such as xylene, CH_2Cl_2, THF, Et_2O, and toluene were tested in this reaction (entries 1–5, Table 3). Finally, reaction in xylene led to an optimal combination of 95% yield and 93% ee.

Under these optimized conditions (that is, **6c**, Et_3N, 0.1 M of substrate in xylene at room temperature), various salicylaldehyde-derived substrates were tested and the results are summarized in Table 4. Substrates **9b–d** bearing electron-donating groups (5-Me, 5-MeO, 4-MeO, entries 2–4, Table 4) on the salicylaldehyde-structure were well tolerated and led to their corresponding chromanone derivatives in good to excellent yields (87–98%) and generally high ees (88–97%). It should be noted that the reaction did not occur when substrate **9e** was used under the standard conditions. When KHMDS was used instead of Et_3N under the standard conditions, substrate **9e** underwent the intramolecular Stetter reaction affording the desired product in 56% yield with 95% ee (entry 5, Table 4). When substrates **9f–g** containing substituents adjacent to the linker were used, the reactions ran smoothly with high yield but moderate to good enantioselectivities (entries 6–7, Table 4). The reaction of substrates **9h–i** bearing weak electron-drawing groups (5-Cl or 5-Br, entries 8–9, Table 4) led to their desired products in excellent yields but with relatively low ees (78%). The sulfur-tethered substrate **9j** gave a moderate yield (70%) with excellent ee (89%) (entry 10, Table 4). When substrate **9k** bearing 5-NO_2 group was used, the desired product was obtained in 90% yield but with no enantioselectivity (entry 11, Table 4). Substrate **9l** which led to a five-membered ring was also examined and the desired product **10l** was obtained also in racemic (entry 12, Table 4). In both cases, they were also known to be challenging substrates in the literature probably due to the ready racemization of the products.[4a] Notably, in some cases, running the reaction for a prolonged time will cause a certain degree of racemization of the product.

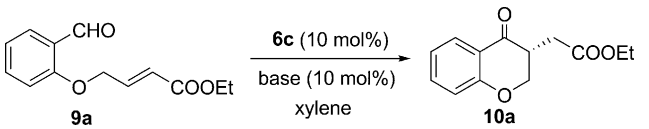
Table 1 Screening of different catalysts



entry[a]	catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	**6a**	36	60	51
2	**6b**	36	43	68
3	**6c**	0.6	95	85
4	**6d**	36	17	10
5[d]	**6c**	0.6	95	82

[a] Reaction conditions: 0.1 M solution, addition of **9a** to the prior generated catalyst. [b] Isolated yields. [c] Determined by chiral HPLC (Daicel Chirapak AD-H). [d] 10 mol% triazolium salt and 10 mol% KHMDS were used.

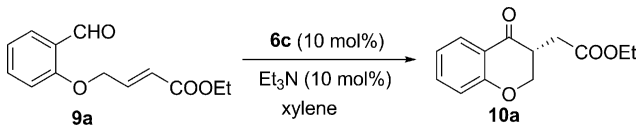
Table 2 Screening of bases



entry[a]	base	time (h)	yield (%)[b]	ee (%)[c]
1	KHMDS	0.6	95	82
2	NaHMDS	1.3	97	85
3	LiHMDS	48	56	90
4	DBU	4	90	87
5	DIEA	85	90	93
6	Et_3N	16	95	93

[a] Reaction conditions: 0.1 M solution, addition of **9a** to the prior generated catalyst. [b] Isolated yields. [c] Determined by chiral HPLC (Daicel Chirapak AD-H).

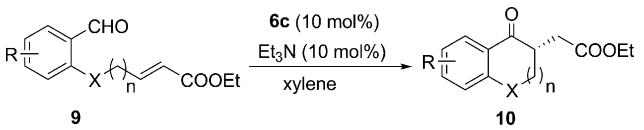
Table 3 Screening of solvents



entry[a]	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	xylene	16	95	93
2	CH_2Cl_2	65	82	74
3	Et_2O	52	79	80
4	toluene	22	95	88
5	THF	42	93	87

[a] Reaction conditions: 0.1 M solution, addition of **9a** to the prior generated catalyst. [b] Isolated yields. [c] Determined by chiral HPLC (Daicel Chirapak AD-H).

Table 4 Substrate scope for enantioselective intramolecular Stetter reactions



entry[a]	**9**	time (h)	yield (%)[b]	ee (%)[c]
1	**9a** X = O, *n* = 1, R = H	16	95	93
2	**9b** X = O, *n* = 1, R = 5-CH_3	21	98	95
3	**9c** X = O, *n* = 1, R = 5-OCH_3	31	95	88
4	**9d** X = O, *n* = 1, R = 4-OCH_3	26	87	97
5[d]	**9e** X = O, *n* = 1, R = 4-NEt_2	67	56	95
6	**9f** X = O, *n* = 1, R = 3-CH_3	8	98	80
7	**9g** X = O, *n* = 1, R = 3-OCH_3	34	98	81
8	**9h** X = O, *n* = 1, R = 5-Cl	9	98	78
9	**9i** X = O, *n* = 1, R = 5-Br	12	93	78
10	**9j** X = S, *n* = 1, R = H	48	70	89
11	**9k** X = O, *n* = 1, R = 5-NO_2	15	90	0
12	**9l** X = O, *n* = 0, R = H	66	59	0

[a] Reaction conditions: 0.1 M solution, addition of **9** to the prior generated catalyst. [b] Isolated yields. [c] Determined by chiral HPLC. [d] KHMDS was used instead of Et_3N.

In conclusion, we have developed a series of novel bicyclic triazolium salts from readily available (1*R*,2*R*)-DPEN. The NHC catalyst derived from the chiral triazolium salt **6c** and Et_3N is found to be efficient for the enantioselective intramolecular Stetter reaction. In general, excellent yields with up to 97% ee could be obtained for the intramolecular Stetter reaction. Further application of these (1*R*,2*R*)-DPEN derived triazolium salts in other asymmetric reactions are currently under way.

Acknowledgements

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