ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 11110–11112

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Asymmetric construction of trifluoromethylated pyrrolidines *via* Cu(I)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with 4,4,4-trifluorocrotonates†

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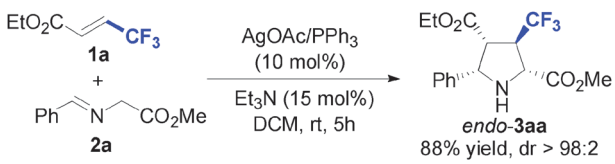
Received 16th July 2011, Accepted 25th August 2011
DOI: 10.1039/c1cc14295j

Trifluoromethylated pyrrolidines have been synthesized *via* catalytic asymmetric 1,3-dipolar cycloaddition with excellent stereoselectivity for the first time. Epimerization of the *endo*-pyrrolidines obtained from *cis*-4,4,4-trifluorocrotonate into the *exo*-pyrrolidines was also revealed.

The chemistry of organofluorine compounds is a rapidly developing area of research due to their wide range of applications in a number of important fields such as drug discovery and materials science.[1] Amongst organofluorine molecules, chiral trifluoromethylated compounds play a unique and significant role in agricultural and medicinal chemistry, as they often impart enhanced biological activity, metabolic stability, binding interaction, or other desirable changes in physical properties to drug molecules.[2] As a consequence, extensive studies have been conducted on the exploitation of the efficient methods for the asymmetric synthesis of such compounds.[2] In recent years, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes[3] has proven to be the diversity-oriented synthesis (DOS)[4] for biologically active pyrrolidine derivatives bearing multiple stereogenic centers in good yields and moderate to high enantio-/diastereoselectivities. Although various electron-deficient alkenes have been applied as dipolarophiles for this transformation, most of them are limited to maleates, fumarates, maleimides, acrylates, nitroalkenes and vinyl phenyl sulfones.[3] However, the easily available *trans*-trifluorocrotonate, which was used as starting building blocks in the synthesis of many fluorine-containing compounds,[5] has seldom been employed as dipolarophiles in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides. To the best of our knowledge, only limited racemic examples have been reported involving *trans*-trifluorocrotonate as the dipolarophile so far.[6] For example, Bonnet-Delpon and co-workers addressed that highly *endo*-selective trifluoromethylated pyrrolidines were successfully achieved *via* 1,3-dipolar cycloaddition of *trans*-trifluorocrotonate with azomethine ylides in the presence of stoichiometric amounts of AgOAc.[6] Subsequently, the initial attempt to access the optically active trifluoromethylated pyrrolidines was reported by the same group employing a chiral azomethine ylide through a chiral-auxiliary-induced 1,3-dipolar cycloaddition reaction.[7] Nevertheless, quite limited progress has been made in the directly catalytic asymmetric approach to access those compounds. Therefore, the development of a catalytic method for the straightforward synthesis of enantio-enriched pyrrolidines bearing the trifluoromethyl group is in high demand. Herein, we communicated the first catalytic asymmetric synthesis of trifluoromethylated pyrrolidines *via* 1,3-dipolar cycloaddition of azomethine ylides to *trans*- and *cis*-trifluorocrotonates with high yield, excellent diastereo- and enantioselectivity. Epimerization of the kinetically favored *endo*-pyrrolidines into the thermodynamically favored *exo*-pyrrolidines was also revealed.

Our initial studies began with the reaction of *trans*-ethyl trifluorocrotonate (**1a**) with *N*-benzylidene glycine methyl ester (**2a**) in the presence of 10 mol% AgOAc/PPh_3 and 15 mol% Et_3N to probe the possibility of employing catalytic amounts of the metal complex as the catalyst. To our delight, the AgOAc/PPh_3 complex exhibited high catalytic efficiency, and the reaction was finished in less than 5 h at room temperature affording the highly *endo*-selective trifluoromethylated pyrrolidine (**3aa**) in 88% yield (Scheme 1), which is comparable with the result achieved by using stoichiometric amounts of AgOAc.[6]

Encouraged by this promising result, we then conducted the asymmetric reaction to evaluate the enantioselectivity using several commercially available chiral ligands such as Monophos (**L1**) and BINAP (**L2**), both of which exhibited excellent results in the catalytic asymmetric 1,3-dipolar cycloaddition



Scheme 1 AgOAc/PPh_3-catalyzed 1,3-dipolar cycloaddition of imino ester **2a** with *trans*-4,4,4-trifluorocrotonate **1a**.

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† Electronic supplementary information (ESI) available: Experimental section. CCDC 827404 and 827405. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc14295j

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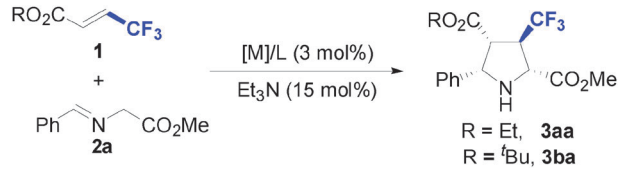
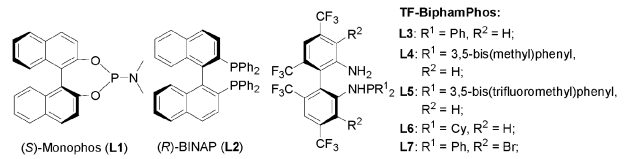
Table 1 Screening studies of the catalytic asymmetric 1,3-dipolar cycloaddition of imino ester **2a** with *trans*-4,4,4-trifluorocrotonates **1**[a]



Entry	L	[M]	Solvent	R	T/°C	Yield[b] (%)	ee[c] (%)
1	**L1**	AgOAc	DCM	Et (**1a**)	rt	85	3
2	**L1**	$CuBF_4$	DCM	Et (**1a**)	rt	78	6
3	**L2**	AgOAc	DCM	Et (**1a**)	rt	54	50
4	**L2**	$CuBF_4$	DCM	Et (**1a**)	rt	35	60
5	**L3**	AgOAc	DCM	Et (**1a**)	rt	85	10
6	**L3**	$CuBF_4$	DCM	Et (**1a**)	rt	88	23
7	**L4**	$CuBF_4$	DCM	Et (**1a**)	rt	85	59
8	**L5**	$CuBF_4$	DCM	Et (**1a**)	rt	37	35
9	**L6**	$CuBF_4$	DCM	Et (**1a**)	rt	70	63
10	**L7**	$CuBF_4$	DCM	Et (**1a**)	rt	85	78
11	**L7**	$CuBF_4$	THF	Et (**1a**)	rt	85	59
12	**L7**	$CuBF_4$	EtOAc	Et (**1a**)	rt	35	50
13	**L7**	$CuBF_4$	MeCN	Et (**1a**)	rt	80	35
14	**L7**	$CuBF_4$	PhMe	Et (**1a**)	rt	Trace	—
15[d]	**L7**	$CuBF_4$	DCM	Et (**1a**)	0	85	83
16[e]	**L7**	$CuBF_4$	DCM	Et (**1a**)	−20	82	86
17[f]	**L7**	$CuBF_4$	DCM	Et (**1a**)	−40	45	85
18	**L7**	$CuBF_4$	DCM	*t*-Bu (**1b**)	−20	85	93

[a] All reactions were carried out with 0.23 mmol of **1** and 0.35 mmol of **2a** in 2 mL solvent for 0.5–1 h. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] Ee and >98 : 2 dr was determined by chiral HPLC analysis. [d] In 3 h. [e] In 5 h. [f] In 10 h.

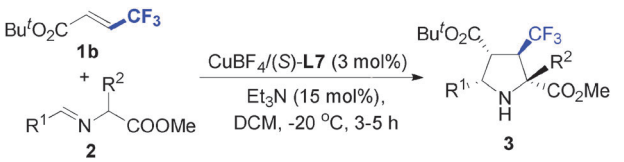


reaction.[3] Ag(I) or Cu(I)/Monophos complexes showed poor enantio-selectivity for this transformation although the catalytic activity and diastereoselectivity were satisfied (Table 1, entries 1 and 2). Combined with Ag(I) or Cu(I) salts the bisphosphine ligand BINAP exhibited a little better asymmetric induction but with relatively low conversion (Table 1, entries 3 and 4). Then, a series of TF-BiphamPhos ligands[8] developed in this laboratory were next screened in order to identify a more efficient catalyst system. In general, copper salts gave better enantioselectivity than silver salts, and the adduct **3aa** was achieved with good yield (88%), excellent diastereoselectivity (>98 : 2) and moderate enantioselectivity (23%) when using the $Cu(CH_3CN)_4BF_4$/**L3** complex as the catalyst (Table 1, entry 6). Further ligands survey revealed that ligand **L7** bearing two bromine at the 3,3′-position of the TF-BIPHAM backbone was the most promising, and provided *endo*-**3aa** as the sole product in 85% yield and 78% ee (Table 1, entry 10). The solvent effect was also studied, CH_2Cl_2 was revealed to be the best solvent in terms of the yield and enantioselectivity while PhMe was not suitable for this reaction (Table 1, entries 10–14). Reducing the reaction temperature from rt to 0 °C and −20 °C led to completed reaction with 83% and 86% ee, respectively (Table 1, entries 15 and 16). Further lowering the temperature had detrimental effect on the reactivity and enantioselectivity (Table 1, entry 17). Finally, the effect of the ester functional group of **1** was also investigated to further improve the enantioselectivity. Replacing the ethyl group of *trans*-trifluorocrotonate with the bulky *tert*-butyl ester (**1b**) led to 93% ee without loss of diastereoselectivity (Table 1, entry 18).

Having established the optimal reaction conditions, we then investigated a series of representative imino esters **2** derived from glycinate to test the substrate scope. As shown in Table 2, a wide array of imino esters derived from aromatic aldehyde reacted smoothly with *trans*-4,4,4-trifluorocrotonate **1b** affording the desired *endo*-adducts in excellent diastereoselectivities and good enantioselectivities (Table 2, entries 1–10). It appears that the position and the electronic property of the substituents on the aromatic rings have very limited effect on the enantio-selectivities. It is noteworthy that comparable results were still achieved for the sterically hindered *ortho*-substituted imino esters **2c**, **2f** and **2h** in terms of selectivity and reactivity (Table 2, entries 3, 6 and 8). Additionally, the heteroaryl substituted imino ester **2k** was also tolerated in this transformation leading to 90% yield and 88% ee[9] (Table 2, entry 11). Imino ester **2l** derived from (±)-alanine also worked well affording the desired *endo*-**3bl** bearing a quaternary stereogenic center[10] with 94% ee (Table 2, entry 12).

Having succeeded in the asymmetric 1,3-dipolar cycloaddition of imino ester with *trans*-4,4,4-trifluorocrotonate, we then investigated the behavior of *cis*-trifluorocrotonate under the optimized reaction conditions (Table 3). Reaction of *cis*-4,4,4-ethyl trifluorocrotonate[11] **1c** with glycine-derived imino esters bearing electron-neutral, electron-deficient and electron-rich groups on the aryl ring delivered the expected *endo*-adducts **4** in good yield with excellent diastereo- and enantioselectivity (98–99% ee) (Table 3, entries 1–3). For the (±)-alanine derived imino ester, 89% ee was also achieved for the desired cyclo-adduct **4cl** (Table 3, entry 4).

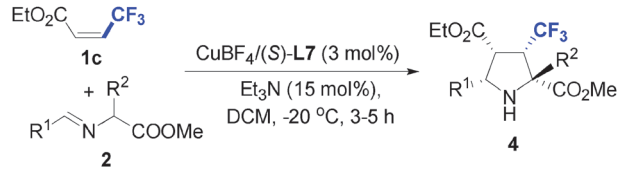
Table 2 Substrate scope of Cu(I)/**L7**-catalyzed asymmetric 1,3-dipolar cycloaddition of various imino esters **2** with *trans-tert*-butyl 4,4,4-trifluorocrotonate **1b**[a]



Entry	R^1	R^2	3	Yield[b] (%)	ee[c] (%)
1	Ph (**2a**)	H	**3ba**	82	93
2	*p*-Me-Ph (**2b**)	H	**3bb**	72	92
3	*o*-Me-Ph (**2c**)	H	**3bc**	87	93
4	*m*-Me-Ph (**2d**)	H	**3bd**	88	90
5	*p*-MeO-Ph (**2e**)	H	**3be**	88	99
6	*o*-MeO-Ph (**2f**)	H	**3bf**	74	95
7	*p*-Cl-Ph (**2g**)	H	**3bg**	76	94
8	*o*-Cl-Ph (**2h**)	H	**3bh**	85	94
9	*m*-Cl-Ph (**2i**)	H	**3bi**	80	91
10	*p*-Br-Ph (**3j**)	H	**3bj**	83	92
11	2-furyl (**2k**)	H	**3bk**	90	88
12[d]	Ph (**2l**)	Me	**3bl**	65	94

[a] All reactions were carried out with 0.23 mmol of **1** and 0.35 mmol of **2a** in 2 mL solvent for 0.5–1 h. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] Ee and >98 : 2 dr was determined by chiral HPLC analysis. [d] Room temperature, 10 h.

Table 3 Cu(I)/(*S*)-**L7**-catalyzed asymmetric 1,3-dipolar cycloaddition of imino esters **2** with *cis*-ethyl 4,4,4-trifluorocrotonate **1c**[a]

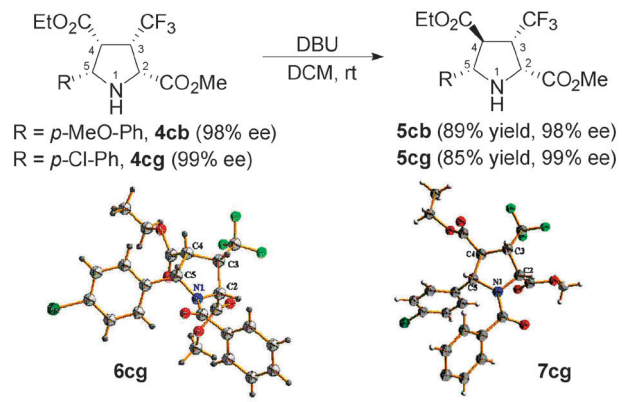


Entry	R^1 (**2**)	R^2	**4**	Yield[b] (%)	dr[c]	ee[c] (%)
1	Ph (**2a**)	H	**4ca**	87	96 : 4	99
2	*p*-MeO-Ph (**2b**)	H	**4cb**	82	>98 : 2	98
3	*o*-Cl-Ph (**2g**)	H	**4cg**	78	96 : 4	99
4[d]	Ph (**2l**)	Me	**4cl**	83	>98 : 2	89

[a] All reactions were carried out with 0.23 mmol of **1** and 0.35 mmol of **2a** in 2 mL solvent for 0.5–1 h. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] Ee and dr >98 : 2 dr was determined by chiral HPLC analysis. [d] Room temperature, 10 h.

Interestingly, we found that *endo*-adducts **4cb** and **4cg** from *cis*-ethyl 4,4,4-trifluorocrotonate **1c** were readily epimerized to *exo*-**5cb** and **5cg** without loss of enantio- and diastereomeric excess when stirred with a stoichiometric amount of DBU in DCM at room temperature (Scheme 2). To determine the relative and absolute configuration of cycloadduct **4cg** and its epimer **5cg**, the derived amides **6cg** and **7cg** were synthesized *via* a simple benzoylation protocol. X-Ray analysis of the two crystals revealed (2*R*,3*S*,4*R*,5*S*) and (2*R*,3*S*,4*S*,5*S*)-configuration for **6cg** and **7cg**, respectively, and therefore also for the corresponding moieties in *endo*-**4cg** and *exo*-**5cg** (Scheme 2).§

From these experimental results, we proposed that with *cis*-ethyl 4,4,4-trifluorocrotonate as the dipolarophile 3,4-*cis*-substituted *endo*-**4** was kinetically favored, and the epimerized 3,4-*trans*-substituted *exo*-**5** was the thermodynamic product. Cycloadduct *endo*-**3bg** obtained from *trans*-trifluorocrotonate was also tested under the same conditions, however, no epimerization occurred probably because the two substituents on positions 3 and 4 of the corresponding pyrrolidine ring in **3bg** have already been oriented in thermodynamically favored *trans* geometry. It must be noted that the epimerized pyrrolidines **5cb** and **5cg**, which correspond to the *exo*-cycloadducts when employing *trans*-ethyl 4,4,4-trifluorocrotonate as the dipolarophile, cannot be prepared directly *via* 1,3-dipolar cycloaddition even in the racemic version.[6]



Scheme 2 Epimerization of cycloadducts **4cb** and **4cg** and X-ray structures of the corresponding benzoylated **6cg** and **7cg**.

In summary, we have developed the first catalytic asymmetric synthesis of trifluoromethylated pyrrolidines *via* Cu(I)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with *trans* and *cis*-4,4,4-trifluorocrotonates. This catalytic system exhibited high reactivity, excellent diastereoselectivity, good enantioselectivity and broad substrate scope. Highly efficient epimerization of the kinetically favored *endo*-pyrrolidines from *cis*-4,4,4-trifluorocrotonate into the thermodynamically favored *exo*-pyrrolidines was also revealed. The ready availability of the starting materials and the great importance of the chiral trifluoromethyl compounds make the current methodology particularly interesting in synthetic chemistry. Further investigations of the scope and synthetic application of this methodology are underway.

This work is supported by the NSFC (20972117), NCET-10-0649, IRT1030, 973 program (2011CB808600), and the Fundamental Research Funds for the Central Universities.

Notes and references

§ For (2*R*,3*S*,4*R*,5*S*)-**6cg**: $C_{23}H_{21}ClF_3NO_5$, M_r = 483.86, T = 293 K, orthorhombic, space group $P2_12_12_1$, a = 8.6745(12), b = 13.3919(18), c = 19.262(3) Å, V = 2237.6(5) Å^3, Z = 4, 12 954 reflections measured, 3670 unique (R_{int} = 0.0353) which were used in all calculations. The final wR_2 = 0.0845(all data), Flack χ = 0.08(7). For (2*R*,3*S*,4*S*,5*S*)-**7cg**: $C_{23}H_{21}ClF_3NO_5$, M_r = 483.86, T = 293 K, orthorhombic, space group $P2_12_12_1$, a = 14.7950(17), b = 15.6582(17), c = 20.390(2) Å, V = 4723.6(9) Å^3, Z = 8, 26 602 reflections measured, 6467 unique (R_{int} = 0.0422) which were used in all calculations. The final wR_2 = 0.0945 (all data), Flack χ = −0.02(6). CCDC 827404 (**6cg**), CCDC 827405 (**7cg**).

1 *Fluorine in Medicinal Chemistry and Chemical Biology*, ed. I. Ojima, Wiley-Blackwell, New York, 2009.

2 (*a*) *Fluorine Containing Amino Acids—Synthesis and Properties*, ed. V. P. Kukhar and V. A. Soloshonok, Wiley, Chichester, 1995; (*b*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2010, **111**, 455.

3 For recent reviews about 1,3-dipolar cycloaddition reactions of azomethine ylides, see: (*a*) B. Engels and M. Christl, *Angew. Chem., Int. Ed.*, 2009, **48**, 7968; (*b*) L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887; (*c*) M. Alvarez-Corral, M. Munoz-Dorado and I. Rodrıguez-Garcıa, *Chem. Rev.*, 2008, **108**, 3174; (*d*) J. Adrio and J. C. Carretero, *Chem. Commun.*, 2011, **47**, 6874.

4 (*a*) S. L. Schreiber, *Science*, 2000, **287**, 1964; (*b*) C. Chen, X. Li and S. L. Schreiber, *J. Am. Chem. Soc.*, 2003, **125**, 10174.

5 (*a*) F. Zhang, Z.-J. Liu and J.-T. Liu, *Tetrahedron*, 2010, **66**, 6864; (*b*) J. L. Wang, K. Aston, D. Limburg, C. Ludwig, A. E. Hallinan, F. Koszyk, B. Hamper, D. Brown, M. Graneto, J. Talley, T. Maziasz, J. Masferrer and J. Carter, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7164; (*c*) B.-L. Wang, F. Yu, X.-L. Qiu, Z.-X. Jiang and F.-L. Qing, *J. Fluorine Chem.*, 2006, **127**, 580; (*d*) O. O. Fadeyi and C. O. Okoro, *Tetrahedron Lett.*, 2008, **49**, 4725.

6 D. Bonnet-Delpon, A. Chennoufi and M. H. Rock, *Bull. Soc. Chim. Fr.*, 1985, **132**, 402.

7 J.-P. Bégué, D. Bonnet-Delpon, A. Chennoufi, M. Ourévitch, K. S. Ravikumar and A. H. Rock, *J. Fluorine Chem.*, 2001, **107**, 275.

8 C.-J. Wang, G. Liang, Z.-Y. Xue and F. Gao, *J. Am. Chem. Soc.*, 2008, **130**, 17250.

9 No cycloaddition was observed when an alkyl substituted imino ester was tested under the same reaction conditions.

10 For recent reviews, see: *Quaternary Stereocenters Challenges and Solutions for Organic Synthesis*, ed. J. Christoffers and A. Baro, Wiley-VCH, Weinheim, 2005.

11 (*a*) B. C. Hamper, *Org. Synth.*, 1998, **49**, 1430; (*b*) J. Leroy, N. Fischer and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1281.

