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Organocatalyzed Regio- and Enantioselective Allylic Trifluoromethylation of Morita–Baylis–Hillman Adducts Using Ruppert–Prakash Reagent

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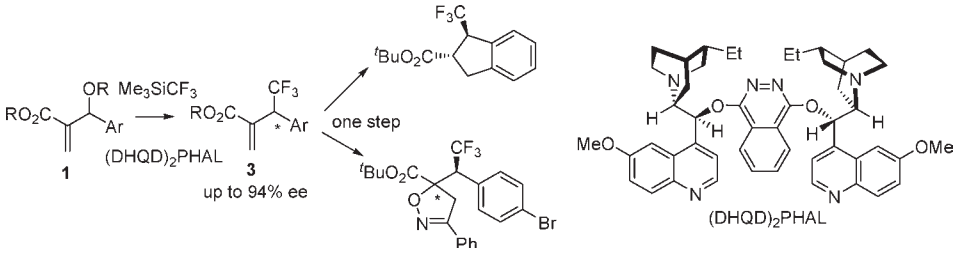
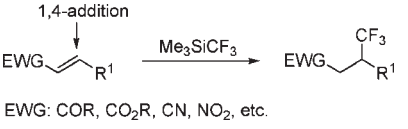
ABSTRACT



The organocatalyzed regioselective allylic trifluoromethylation of Morita–Baylis–Hillman adducts using Ruppert–Prakash reagent was achieved in high to excellent yields via a successive S_N2'/S_N2' mode for the first time. The reaction was extended to the asymmetric allylic trifluoromethylation by the use of a bis-cinchona alkaloid catalyst with high enantioselectivities up to 94% ee.

Ruppert's reagent,[1] (trifluoromethyl)trimethylsilane (Me_3SiCF_3), later renamed as the Ruppert–Prakash reagent, is now firmly established as a powerful tool for direct construction of C–CF_3 bond formation. The Ruppert–Prakash reagent has been extensively studied for the synthesis of trifluoromethyl-containing compounds,[2] particularly in the fields of medicinal chemistry and material science ever since the first report on the trifluoromethylation of aldehydes by using tetrabutylammonium fluoride by Prakash and Olah.[3] A large number of nucleophilic trifluoromethylation of carbonyls and imines using Me_3SiCF_3 have been investigated;[2] however, the addition of Me_3SiCF_3 to electron-deficient alkenes as represented by the Michael addition reaction remains a challenge, even in a racemic, nonstereoselective fashion (Scheme 1).

Scheme 1. Nucleophilic Trifluoromethylation of Electron-Deficient Alkenes



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(1) (a) Ruppert, I.; Shlich, K; Volbach, W. *Tetrahedron Lett.* **1984**, *24*, 2195. (b) Pawelke, G. J. *J. Fluorine Chem.* **1989**, *42*, 429.

(2) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (b) Billard, T.; Langlois, B. R. *Eur. J. Org. Chem.* **2007**, 891. (c) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (d) Gritsenko, R. T.; Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2009**, *50*, 2994. (e) Levin, V. V.; Kozlov, M. A.; Song, Y. H.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2008**, *49*, 3108. (f) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2597. (g) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. (h) Shimizu, R.; Egami, H.; Nagi, T.; Chae, J.; Hamashima, Y.; Sodeoka, M. *Tetrahedron Lett.* **2010**, *51*, 5947. (i) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538.

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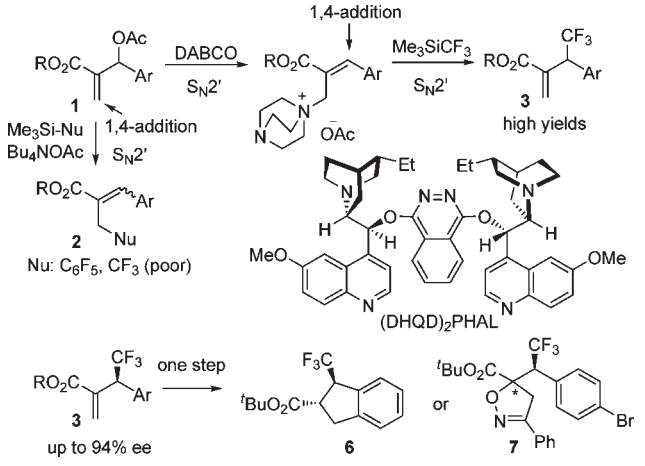
Only a few examples of Michael and Michael-type reactions have been reported, but their substrate generalities are quite narrow.[4] Dilman and co-workers reported a Michael-type addition of Me_3SiCF_3 to highly electrophilic alkenes bearing either two germinal nitrile groups or Meldrum' acids.[5a,b] The reactions were then extended to the addition of C_6F_5-substituted silanes to acylated Morita–Baylis–Hillman adducts **1** using catalytic amounts of tetrabutylammonium acetate affording C_6F_5-substituted products **2** via the S_N2' substitution mode at the terminal double bond in good yields; moreover, the reaction of acylated Morita–Baylis–Hillman adduct 1 using Me_3SiCF_3 instead is poor[5c,6] (Scheme 2, from **1** to **2**). Our laboratory has been engaged for several years in a program that utilizes Me_3SiCF_3 for the efficient synthesis of trifluoromethylated compounds.[7] We disclose herein the first example of regio-selective nucleophilic allylic trifluoromethylation of acylated Morita–Baylis–Hillman adducts **1** with Me_3SiCF_3 catalyzed by tertially amine via a successive S_N2'/S_N2' mode, addition–elimination/addition–elimination, to provide medicinally attractive synthons, α-methylene β-trifluoromethyl esters **3** in high to excellent yields (Scheme 2, from **1** to **3**). We also achieved an organocatalyzed enantioselective allylic trifluoromethylation of Morita–Baylis–Hillman adducts with Me_3SiCF_3 by commercially available cinchona alkaloid, $(DHQD)_2PHAL$, to furnish chiral **3** in high enantioselectivities up to 94% ee, for the first time. The β-trifluoromethyl esters **3** obtained here can be efficiently converted into interesting carbocyclic and heterocyclic compounds without any loss of the enantiomeric purities of the starting substrates (Scheme 2).

Scheme 2. Two Modes of Allylic Trifluoromethylation of Morita–Baylis–Hillman Adducts, S_N2' Mode (from **1** to **2** known[5c,6]) and Successive S_N2'/S_N2' Mode (from **1** to **3**, unknown, this work), and Its Application to the Enantioselective Synthesis of Carbo- and Heterocyles **6**, **7**



(4) (a) Sevenard, D. V.; Sosnovskikh, V. Y.; Kolomeitsev, A. A.; Knigsmann, M. H.; Roschenthaler, G. V. *Tetrahedron Lett.* **2003**, *44*, 7623. (b) Sosnovskikh, V. Y.; Usachev, B. I.; Sevenard, D. V.; Roschenthaler, G. V. *J. Org. Chem.* **2003**, *68*, 7747. (c) Sosnovskikh, V. Y.; Sevenard, D. V.; Usachev, B. I.; Roshenthler, G. V. *Tetrahedron Lett.* **2003**, *44*, 2097. (d) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848.

Our initial investigation started with finding out a suitable catalyst on the successive S_N2'/S_N2' allylic trifluoromethylation of Morita-Baylis-Hillman acetate **1a** with Me_3SiCF_3 (Table 1). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), Et_3N, PPh_3, and 4-dimethylaminopyridine (DMAP) were found to be ineffective in the trifluoromethylation reaction in THF (entries 1–4). In contrast, the use of a catalytic amount of quinuclidine proceeded readily at room temperature to give trifluoromethylated product **3a** in 75% yield (entry 5). The trifluoromethyl substituent was regioselectively introduced at the benzylic position via successive S_N2'/S_N2' substitution and an addition to the terminal alkene via the S_N2' mode was not observed. The yield of **3a** improved to 77% when 1,4-diazabicyclo-[2.2.2]octane (DABCO) was used (entry 6). Solvent optimization was performed next. We attempted to use CH_2Cl_2, toluene or DMF as the solvent, but the results did not improve (Table 1, entries 7–9). The use of 2 equivalents of Me_3SiCF_3 improved the yield of **3a** to 96% (Table 1, entry 10).

With the optimized conditions established, the scope of substrates in regioselective, successive S_N2'/S_N2' allylic trifluoromethylation was investigated (Table 2). A series of Morita–Baylis–Hillman acetates **1b–j** with a variety of substituents on the aromatic ring, such as chloro, bromo, methyl, methoxy, and nitro group were nicely converted into the corresponding successive S_N2'/S_N2' mode trifluoromethylated products **3b–j** in up to 99% yields (entries 1–9). The reaction of sterically demanding naphthyl moiety and heteroaryl moieties also proceeded well in 85–92% yields (entries 10–13). Multiply substituted aryl substrates such as **1o** and **1p** gave allylic trifluoromethylated products **3o** and **3p** regioselectively in 93% yields (entries 14 and 15). A series of sterically less demanding methyl esters **1q–s** were also converted to the desired compounds **3q–s** in excellent yields, without any adducts from a nucleophilic CF_3 attack on the carbonyl carbon observed in the previous report.[5c,6] A substrate with alkyl substitution instead of the aryl substitution, that is, *tert*-butyl 3-acetoxy-2-methylenebutanoate, was also examined for

(5) (a) Dilman, A. D.; Levin, V. V.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2008**, *49*, 4352. (b) Zemtsov, A. A.; Levin, V. V.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A. *Tetrahedron Lett.* **2009**, *50*, 2998. (c) Zemtsov, A. A.; Levin, V. V.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Tartakovsky, V. A.; Hu., J. *Eur. J. Org. Chem.* **2010**, 6779.

(6) Reaction of **1q** with Me_3SiCF_3 inefficiently provides an 1/1 mixture of S_N2'-substitution adduct and 1,2-adduct in 30% combined yield.

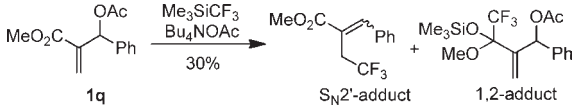


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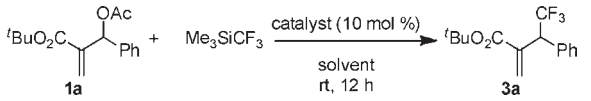
Table 1. Optimization of the Reaction Conditions[a]



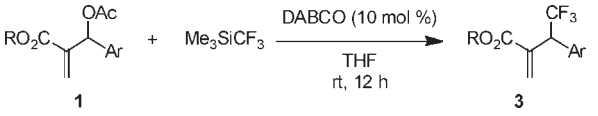
entry	catalyst	solvent	yield (%)
1	DBU	THF	0
2	Et_3N	THF	0
3	PPh_3	THF	0
4	DMAP	THF	Trace
5	Quinuclidine	THF	75
6	DABCO	THF	77
7	DABCO	CH_2Cl_2	32
8	DABCO	Toluene	27
9	DABCO	DMF	0
10[b]	DABCO	THF	96

[a] Reactions were carried out using **1a** (1.0 equiv), Me_3SiCF_3 (1.2 equiv), catalyst (10 mol %) in solvent at room temperature for 12 h unless otherwise noted. [b] Me_3SiCF_3 (2.0 equiv) was used.

allylic trifluoromethylation under the same reaction conditions, but complex mixture was resulted. To our knowledge, this is the first example of allylic trifluoromethylation of Morita–Baylis–Hillman adducts via the successive S_N2'/S_N2'mode.

Next, a preliminary investigation of asymmetric catalysis was conducted (Table 3). Asymmetric allylic alkylation (AAA)[8] is one of the most powerful tools for making enantiomeric compounds and for developing creative synthetic methodologies in the synthesis of optically active natural products. Such a reaction is in general most actively investigated by transition-metal catalysts represented by the Tsuji–Trost reaction.[8] On the other hand, recent advances in asymmetric organocatalysis have induced another strategy for the asymmetric allylic alkylation or substitution of Morita–Baylis–Hillman adducts using various carbon- or heterocentered nucleophiles.[9] For the organocatalyzed asymmetric allylic alkylation based

Table 2. Trifluoromethylation of Morita–Baylis–Hillman Acetates[a]



entry	1	R	Ar	3	yield[b] (%)
1	**1b**	^{t}Bu	3-ClC_6H_4	**3b**	98
2	**1c**	^{t}Bu	4-ClC_6H_4	**3c**	95
3	**1d**	^{t}Bu	2-BrC_6H_4	**3d**	67
4	**1e**	^{t}Bu	3-BrC_6H_4	**3e**	99
5	**1f**	^{t}Bu	4-BrC_6H_4	**3f**	98
6	**1g**	^{t}Bu	3-MeC_6H_4	**3g**	99
7	**1h**	^{t}Bu	4-MeC_6H_4	**3h**	91
8	**1i**	^{t}Bu	3-$MeOC_6H_4$	**3i**	92
9	**1j**	^{t}Bu	4-$NO_2C_6H_4$	**3j**	87
10	**1k**	^{t}Bu	1-Naphthyl	**3k**	85
11	**1l**	^{t}Bu	2-Naphthyl	**3l**	92
12	**1m**	^{t}Bu	2-Furyl	**3m**	87
13	**1n**	^{t}Bu	2-Pyridyl	**3n**	85
14	**1o**	^{t}Bu	3,4-$Cl_2C_6H_3$	**3o**	93
15	**1p**	^{t}Bu	3,5-Br_2-4-$MeOC_6H_2$	**3p**	93
16	**1q**	Me	Ph	**3q**	96
17	**1r**	Me	4-$MeOC_6H_4$	**3r**	90
18	**1s**	Me	4-BrC_6H_4	**3s**	96

[a] Reactions were carried out using **1a** (1.0 equiv), Me_3SiCF_3 (2.0 equiv), DABCO (10 mol %) in THF at room temperature for 12 h unless otherwise noted. [b] Isolated yield.

on carbon–carbon bond-formation, allylic alkylations with soft nucleophiles, including 1,3-dicarbonyl compounds and dicyanoalkenes, have been reported; however, organocatalyzed allylic alkylations with a hard nucleophile, the CF_3 anion, have not been reported. In this context, we first attempted our allylic trifluoromethylation reaction of **1a** with Me_3SiCF_3 in the presence of a catalytic amount of bis-cinchona alkaloid, $(DHQD)_2PHAL$.[10] Unfortunately, even after heating, no reaction was observed (Table 3, entry 1). After a brief survey of the reaction conditions, Morita–Baylis–Hillman carbonates **4a–d** were found to be effective substrates for the asymmetric allylic trifluoromethylation reaction to furnish the desired chiral α-methylene β-trifluoromethyl esters in high enantioselectivities up to 94% ee, although the conversion was lower than that of racemic condition (entries 2—5). The short list of the enantioselective version of this transformation, however, was carefully chosen to demonstrate sufficient diversity of the present chemistry, which included nonsubstituted aromatic, *o*- or *p*-substituted aromatics with halogenyl moiety, sterically demanding or a sterically less demanding ester group. These results indicated that the substitution of the aromatic ring and ester moiety did not significantly affect the reactivity and enantioselectivity.

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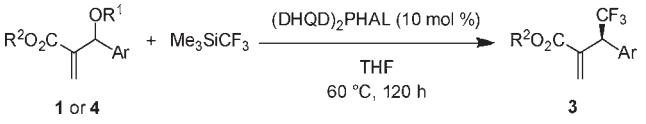
(10) Catalyst and solvent screening are shown in Tables S1 and S2 in the Supporting Information.

The absolute stereochemistry of (*S*)-**3f** was confirmed by X-ray crystallographic analysis of the derivative (1*R*,2*S*)-**7** described in the later part of the text (Figure 1 and Scheme 3) and the absolute stereochemistry of other trifluoromethylated compounds **3** was tentatively assumed by analogy.

Table 3. Enantioselective Trifluoromethylation of Morita–Baylis–Hillman Carbonates[a]



entry	1/4	R^1	R^2	Ar	3	yield[b] (%)	ee (%)
1	**1a**	Ac	^{t}Bu	C_6H_5	**3a**	Trace	ND
2	**4a**	Boc	^{t}Bu	C_6H_5	**3a**	39	92
3	**4b**	Boc	^{t}Bu	2-BrC_6H_4	**3d**	37	88
4	**4c**	Boc	^{t}Bu	4-BrC_6H_4	**3f**	60	90
5	**4d**	Boc	Me	C_6H_5	**3q**	52	94

[a] Reactions were carried out using **1a** (1.0 equiv), Me_3SiCF_3 (5.0 equiv), $(DHQD)_2PHAL$ (10 mol %) in THF at 60 °C for 120 h unless otherwise noted. [b] Isolated yield.

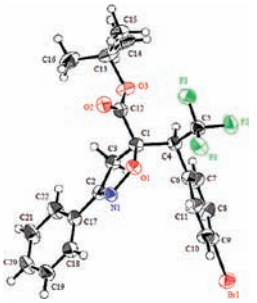
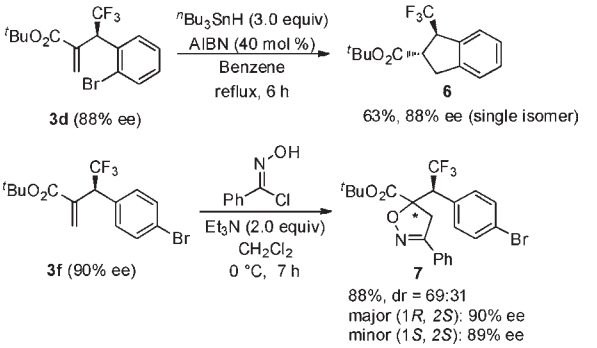


Figure 1. X-ray Crystallographic analysis of (1*R*,2*S*)-**7** (CCDC 827782).

The chiral α-methylene β-trifluoromethyl esters **3** obtained here could be smoothly transformed into biologically attractive carbo- and heterocycles **6** and **7**. Two examples were performed (Scheme 3). First, intramolecular radical cyclization of the allylic trifluoromethylated product **3d** proceeded efficiently in the presence of ^{n}Bu$_3$SnH and AIBN to stereoselectively afford Indane derivative **6**. The relative stereochemistry of **6** was tentatively assigned to be a thermodynamically stable *trans*-configuration by the NMR analysis of **6**. Heterocycle **7**, having a spiro center, was also synthesized as a mixture of diastereoisomers by the 1,3-dipolar cycloaddition reaction of trifluoromethylated product **3f** with chlorobenzaldoxime in the presence of triethylamine in CH_2Cl_2 in 88% yield. In both cases, enantiopurities of the starting substrates **3** were retained.

Scheme 3. Conversion of Chiral α-Methylene β-Trifluoromethyl Esters **3** into Carbo- and Heterocycles **5** and **6**



In summary, the organocatalyzed regioselective allylic trifluoromethylation of Morita–Baylis–Hillman adducts using Ruppert's reagent was achieved in high to excellent yields via a successive S_N2'/S_N2' mode for the first time. The reaction was extended to the asymmetric allylic trifluoromethylation by the use of bis-cinchona alkaloid catalyst with high enantioselectivities up to 94% ee. This should be a powerful protocol for accessing enantiomeric α-methylene β-trifluoromethyl esters that are useful synthetic building blocks for further transformation.

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Supporting Information Available. Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.