Construction of Nonadjacent Stereocenters Containing a Trifluoromethylated Carbon by Organocatalyzed Michael Addition of β-Ketoesters to 2-(Trifluoromethyl)acrylate

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The first enantioselective construction of nonadjacent 1,3-tertiary–quaternary stereocenters containing a trifluoromethylated carbon by cinchona alkaloid-catalyzed Michael addition of β-ketoesters to 2-(trifluoromethyl)acrylate has been achived in high yields with high enantioselectivities up to 97% ee.

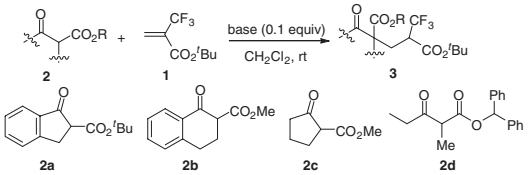
The development of an efficient methodology for the enantiocontrolled synthesis of trifluoromethylated organic compounds has attracted considerable attention, particularly in the field of medicinal chemistry.[1] The main general approaches to the synthesis of these compounds involve (i) the enantioselective direct introduction of a trifluoromethyl group into a certain position of the desired compounds, and (ii) asymmetric reaction using relatively accessible trifluoromethylated compounds as building blocks.[1] Despite the conceptual appeal inherent in the first approach, this is still a challenging task, and the second one has found more ready application in the synthesis of complex molecules. The increasing commercial availability of trifluoromethylated compounds provides the impetus to develop novel asymmetric methodology based on the fluorinated building block strategy.[2] Trifluoropyruvates as building blocks are especially attractive for this purpose, and intensive efforts have been devoted to this area in the last decade.[3] On the other hand, asymmetric reactions using 2-(trifluoromethyl)acrylates as building blocks are relatively few regardless of the easy accessibility of these materials.[4]

The catalytic enantio- and diastereoselective Michael addition or a related reaction is an effective way of generating multiple stereocenters in the products in one step. Methodology for creating 1,2-adjacent stereocenters by this strategy has made significant progress in recent years however, accessing a chiral product with noncontinuous 1,3-nonadjacent stereocenters, particularly in acyclic systems, using a similar strategy is rare.[5] Application of this methodology for the enantioselective synthesis of trifluoromethylated compounds by controlling the noncontinuous, 1,3-nonadjacent stereocenters has not been reported as far as we know. Recently, Deng and co-workers accomplished a one-step and stereoselective construction of nonfluorinated 1,3-tertiary–quaternary stereocenters through the asymmetric Michael addition of cyanoesters with acrylonitriles catalyzed by bifunctional cinchona alkaloids.[5a,5b] In spite of the encouraging high levels of asymmetric control obtained in their paper, further examples of enantioselective reaction for the synthesis of trifluoromethylated compounds have not appeared. We recently reported the construction of adjacent quaternary–quaternary stereocenters containing a trifluoromethylated carbon by asymmetric direct aldol reaction of oxindoles with ethyl trifluoropyruvate catalyzed by cinchona alkaloids.[6] As part of our program related to the foregoing,[6,7] we attempted to construct nonadjacent 1,3-tertiary–quaternary stereocenters containing a tertiary-trifluoromethylated carbon center by cinchona alkaloid-catalyzed Michael addition of β-ketoesters **2** to *tert*-butyl 2-(trifluoromethyl)acrylate (**1**), giving previously unknown trifluoromethylated diesters **3** in high yields with high diastereo- and enantioselectivities up to 97% ee.

Our initial studies focused on the assessment of 2-(trifluoromethyl)acrylate **1** as a Michael acceptor for the reaction with β-ketoesters **2**. 2-(Trifluoromethyl)acrylates are reactive compounds and tend to be polymerized under strong base conditions. Yamazaki, Kitazume, and co-workers overcame the problem by using weaker, nonmetallic nucleophiles such as enamines or malonic esters with triethylamine.[8] However, reaction with β-ketoesters as a Michael donor has not been reported. We therefore were intrigued by the possibility of performing a direct organocatalytic Michael addition reaction of β-ketoesters with 2-(trifluoromethyl)acrylates. *tert*-Butyl indanonecarboxylate (**2a**) was chosen as a prenucleophile for initial studies. In dichloromethane, several bases were screened for this reaction and the results are shown in Table 1. Contrary to our expectation from earlier reports,[8] triethylamine was not particularly effective (Entry 1), and stronger organic bases such as DBU, DABCO, 1,1,3,3-tetramethylguanidine (TMG), and phosphazene base P_1-*t*-Bu [*tert*-butylimino-tris(dimethylamino)phosphorane] were required for effective transformation from **2** with **1** to **3** (Entries 4–7). Self-polymerization of **1** was not observed in any conditions. Inorganic bases were completely ineffective (Entries 2 and 3). The Michael reaction of other β-ketoesters **2b** and **2c** with **1** also proceeded in the presence of DBU (Entries 8 and 9), while the reaction with acyclic substrate **2d** required a longer reaction time to reach completion (Entry 10).

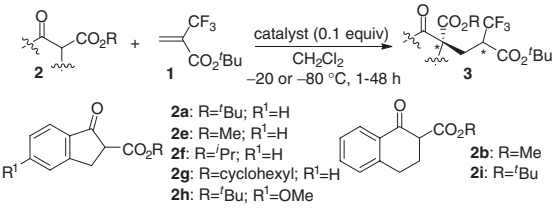
We next attempted the asymmetric variant of this reaction, and commercially available cinchona alkaloids were screened

Table 1. Organo-catalyzed Michael addition of **2** to **1**



Entry	β-Ketoester **2**	Base	Time	Yield/%	de/%
1	**2a**	Et_3N	48 h	47	48/52
2	**2a**	K_2CO_3	72 h	31	52/48
3	**2a**	$NaHCO_3$	72 h	42	52/48
4	**2a**	DBU	15 min	84	48/52
5	**2a**	DABCO	5 h	87	51/49
6	**2a**	TMG	10 min	85	57/43
7	**2a**	P_1-*t*-Bu	72 h	52	37/63
8	**2b**	DBU	2 h	93	44/56
9	**2c**	DBU	5 min	73	45/54
10	**2d**	DBU	60 h	85	58/42

Table 2. Cinchona alkaloid-catalyzed enantioselective Michael addition of β-ketoesters to *tert*-butyl 2-(trifluoromethyl)acrylate



Entry	2	Catalyst	3	Yield/%	de[a]/%	ee[a,b]/%
1[c]	**2a**	Quinine	**3a**	70	56/44	−68
2[c]	**2a**	Quinidine	**3a**	75	58/42	+63
3[c]	**2a**	Cinchonine	**3a**	72	79/21	+86
4[c]	**2a**	Cinchonidine	**3a**	83	71/29	−83
5[c]	**2a**	$(DHQ)_2AQN$	**3a**	83	57/43	−10
6[c]	**2a**	$(DHQD)_2AQN$	**3a**	96	56/44	+2
7[c]	**2a**	$(DHQ)_2PHAL$	**3a**	67	65/35	−39
8[c]	**2a**	$(DHQ)_2PYR$	**3a**	84	54/46	−20
9[d]	**2a**	Cinchonine	**3a**	99	85/15[g]	+93
10[d]	**2a**	Cinchonidine	**3a**	91	74/26	−86
11[e]	**2a**	Cinchonine	**3a**	94	75/25	+97
12[d]	**2e**	Cinchonine	**3e**	88	84/16	+93
13[d]	**2f**	Cinchonine	**3f**	90	86/14	+94
14[d]	**2g**	Cinchonine	**3g**	42	82/18	+90
15[d]	**2h**	Cinchonine	**3h**	93	75/25	+87
16[e]	**2h**	Cinchonine	**3h**	97	61/39[h]	+97
17[f]	**2b**	Cinchonine	**3b**	75	67/33	+40
18[f]	**2i**	Cinchonine	**3i**	55	69/31	+57

[a]Although stereochemistry of **3** is not decided, the absolute configuration at newly generated quaternary carbon center of **3** was tentatively assigned to be R by analogy to the related Michael addition of **2a** or **2e** with methyl or *t*-butyl acrylate (M. Nakajima, S. Yamamoto, Y. Yamaguchi, S. Nakamura, S. Hashimoto, *Tetrahedron* **2003**, *59*, 7307). See SI[9] for details. Resulting two diastereoisomers were difficult to separate on TLC. [b]Ee value of major diastereoisomer of **3** with a sign of its optical rotation. [c]Reaction was carried out at −20 °C. [d]Reaction was carried out at −80 °C. [e]Reaction was carried out in toluene at −80 to −40 °C. [f]Reaction was carried out in 1.0 mL of CH_2Cl_2/toluene = 7/3 at rt. [g]Minor diastereomer of **3a** has an ee value of +83%. [h]Minor diastereomer of **3h** has an ee value of +96%.

as catalysts (Table 2, Entries 1–8). We were pleased to find that the asymmetric Michael addition of **2a** with **1** worked well to give the adduct **3a** in a high yield of 72% with relatively high diastereo- and enantioselectivities of 86% ee, when the reaction was carried out in CH_2Cl_2 at −20 °C in the presence of a catalytic amount of cinchonine (Entry 3). The enantioselectivity of **3a** was increased to 93% ee by lowering the reaction temperature to −80 °C in the presence of cinchonine (Entry 9). It should be noted that the minor diastereomer of **3a** was also isolated with a high enantiomeric excess (83%) (see footnote, Entry 9), and the opposite stereochemistry of the major diastereomer to that observed using cinchonidine catalyst, was obtained by the use of cinchonine as a catalyst (86% ee, Entry 10). The best enantioselectivity for **3a** (97% ee) was observed when the reaction was carried out in toluene, although the diastereoselectivity was decreased slightly (Entry 11). These initial screenings led us to select cinchonine as a catalyst for the enantioselective Michael addition reaction of a number of β-ketoesters **2** with **1** in CH_2Cl_2 or toluene (Entries 12–18). While similarly high diastereo- and enantioselectivities were observed in the Michael addition of a series of indanonecarboxylates with **1** independent of its ester moiety and substitution at benzene ring affording corresponding diesters having 1,3-tertiary–quaternary stereocenters with up to 97% ee (Entries 12–16), both the diastereo- and enantioselectivities of the reaction between tetralone carboxylates with **1** were moderate (Entries 17 and 18). Again, a minor diastereomer **3h** was obtained with a high enantioselectivity of 96% ee (see footnote, Entry 16).

In conclusion, we have investigated an organocatalyzed Michael addition of β-ketoesters **2** with 2-(trifluoromethyl)acrylate **1** to afford trifluoromethylated diesters in which two nonadjacent stereocenters are formed with moderate to high diastereocontrol and enantiocontrol up to 97% ee.[9] Although this methodology has some limitations with substrate generality, to our knowledge, this is the first example of enantioselective Michael addition of β-ketoesters to 2-(trifluoromethyl)acrylates. Application of this methodology to the synthesis of medicinally attractive molecules and further improvement of the enantioselectivity by screening other types of chiral organocatalysts are now in progress.

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9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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