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Room Temperature Asymmetric Allylic Trifluoromethylation of Morita–Baylis–Hillman Carbonates

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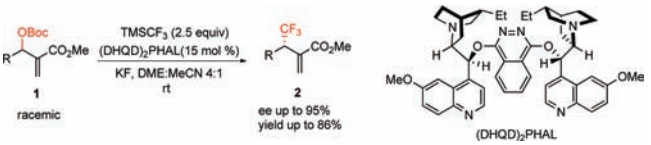
ABSTRACT



(DHQD)$_2$PHAL-catalyzed asymmetric allylic trifluoromethylation of Morita–Baylis–Hillman adducts using a Rupert–Prakash reagent is reported. This transformation provided the S_N2' trifluoromethylated products with good yields and excellent enantioselectivities at room temperature. It was also found that the reaction could be accelerated using acetonitrile as cosolvent.

Trifluoromethylated compounds have gained growing interest owing to their unique physical and chemical properties such as great stability, high electronegativity, and good lipophilicity. These properties may have contributed to the enhanced bioavailability and metabolic stability found in fluorinated pharmaceutical agents,[1] and therefore increasing efforts have been devoted in this particular field.[2] To date, significant progress has been made in the arena of nucleophilic 1,2-trifluoromethylation[3] and α-trifluoromethylation[4] of carbonyl compounds including their asymmetric version.[5] However, the reported methods of introducing a trifluoromethyl group, especially their asymmetric versions, are still at their infancy and cannot meet the growing needs from both pharmaceutical and advanced material industry. To this end, there is a strong need to develop more efficient and convenient trifluoromethylation reactions.

Allylic alkylation is one of the most powerful approaches to construct carbon–carbon and carbon–heteroatom bonds.[6] Recently, the allylic alkylation of Morita–Baylis–Hillman (MBH) adducts catalyzed by organic Lewis base have become an attractive strategy to construct a large variety of multifunctional compounds.[7] Enlightened by these findings, we postulated that (Scheme 1) a Lewis base catalyzed allylic trifluoromethylation could be achieved via a S_N2' reaction. The strong basicity of *tert*-butoxy anion may

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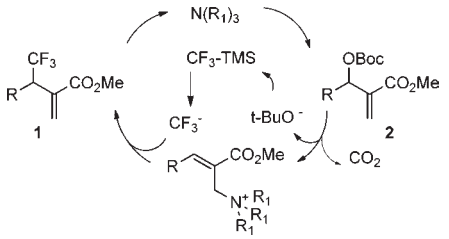
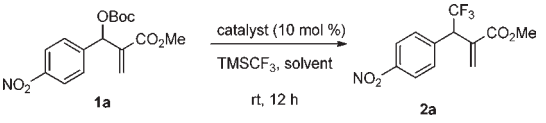
Scheme 1. Proposed Lewis Base Catalyzed Allylic Trifluomethylation of MBH Carbonates



regenerate the hard nucleophilic CF_3 anion *in situ*. During the preparation of this manuscript, Shibata and co-workers reported the first allylic trifluoromethylation of MBH adducts in high yields.[8] The four enantioselective examples they described require long reaction time and elevated temperature (ca. 5 days, 60 °C) and excess of Ruppert reagent (5 equiv). The desired products were isolated with modest yield. Herein, we describe an improved reaction condition for the cinchona alkaloid catalyzed asymmetric allylic trifluoromethylation of MBH carbonates using Ruppert reagent. This method allows the reaction to proceed under room temperature with much improved yield.

Initially, with the Ruppert reagent as the trifluoromethyl source, we examined the reaction using 4-nitro-MBH carbonate (**1a**) as the prototypical substrate and DABCO or Ph_3P as the Lewis base to test our speculated transformation in different solvents (Table 1). To our delight, we found that DABCO smoothly catalyzed the allylic trifluorometylation in DME with very good chemoselectivity and yield. In contrast, no desired product was found when using Ph_3P as catalyst or DMF as solvent. Notably, when palladium-catalyzed allylic alkylation conditions were employed[9] (entries 6 and 7, Table 1), no desired product was found in the reaction mixture. Encouraged by this preliminary result, we envisaged that an appropriate chiral tertiary amine might be able to transfer its chirality to the newly generated allylic carbon bearing a CF_3 group based on the mechanism depicted in Scheme 1. A literature survey led us to cinchona and its derivatives,

Table 1. Identifying Catalyst for the Reaction[a]



entry	catalyst	solvent	yield[c] (%)
1	DABCO	DMF	0
2	DABCO	DME	85
3	none	DME	0
4	PPh_3	DME	0
5	PPh_3	DMF	0
6	$(\eta^3\text{-}C_3H_5PdCl)_2$	DME	0
7[b]	Pd + *i*-Pr PhOX	DME	0

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **1a**, 0.25 mmol of $TMSCF_3$, 0.01 mmol of KF, and 0.01 mmol of catalyst in 0.5 mL of solvent. [b] $(\eta^3\text{-}C_3H_5PdCl)_2$, 0.005 mmol, and (*R*)-(−)-2-[2-(diphenylphosphino)phenyl]-4-isopropyl-2-oxazoline (*i*-Pr PhOX), 0.01 mmol, were used. [c] Isolated yield.

especially $(DHQD)_2PHAL$, which was first reported by Sharpless et al. in asymmetric dihydroxylation reactions.[10] This chiral tertiary amine base is usually treated as an enantiomeric equivalent of DABCO and has been applied in various asymmetric organic transformations.[11] We found that under the same condition as that for DABCO, $(DHQD)_2PHAL$ was a less efficient catalyst. The reaction hardly proceeded to full conversion in DME even after 120 h of stirring at room temperature. However, to our delight, high enantiomeric excess was observed in the trial reactions. Elevating the reaction temperature to 50 °C showed slight acceleration of reaction rate, but the ee dropped from 94% to 79% (entries 1 and 2, Table 2). When this reaction was performed under higher concentration (0.5 M), the reaction could proceed to full conversion with good yield and excellent ee value (95%) at room temperature. Reaction rate could be further accelerated with the substrate concentration reaching 1 M; however, the ee value started to drop to 89%. Considering charge could build up for the key reaction intermediates, we decided to further investigate solvent effects for this transformation.

Solvent screening did show that acetonitrile has significant acceleration effect on this transformation. The reaction could proceed to full conversion within 8 h; however, the ee value was less satisfying (entry 7, Table 2). It is also interesting to note that in this solvent system, when the reaction was performed under lower concentration and catalyst loading, we were still able to drive the reaction to completion within 24 h with some

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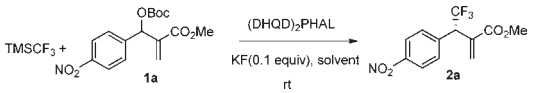
Table 2. Optimization of Reaction Conditions



entry	cat. (mol %)	concn (M)	solvent	time (h)	yield[c]	ee[d] (%)
1	0.2	0.20	DME	120	41	94
2[a]	0.2	0.20	DME	65	40	79
3	0.2	0.50	DME	106	84	95
4	0.2	1.0	DME	72	86	89
5	0.2	1.0	THF	72	53	91
6	0.2	1.0	toluene	72	39	90
7	0.2	1.0	CH_3CN	8	72	74
8	0.2	1.0	DCE	72	48	90
9	0.2	1.0	EtOAc	72	66	87
10	0.2	1.0	dixoane	72	55	93
11	0.2	0.50	CH_3CN	8	85	72
12	0.1	0.30	CH_3CN	14	86	65
13[b]	0.1	0.30	CH_3CN	24	87	78
14	0.1	0.30	PhCN	65	43	76
15	0.1	0.30	$C_5H_{11}CN$	65	51	78
16	none	0.30	CH_3CN	48	0	NT

[a] Reaction was performed at 50 °C. [b] Reaction was performed at 0 °C. [c] Isolated yield. [d] Determined by chiral SFC analysis.

sacrifice of enantioselectivity (entries 11−13, Table 2). Lowering the reaction temperature to 0 °C did not improve the ee value. Other cyano containing solvents such as valeronitrile and benzonitrile failed to show any reaction rate acceleration or enantioselectivity benefit. In order to ensure that the acceleration effect is not a result of the weak nucleophilicity of the cyano group, a blank control reaction was carried out in acetonitrile in the absence of the catalyst, and no detectable product was formed in the reaction. These data suggest that the remarkable rate acceleration of acetonitrile is not due to its weak nucleophilicity, which may have a competitive role against $(DHQD)_2PHAL$, but through the stabilization of the charged transition states.

With the facts that etherate solvent can provide good yield and enantioselectivity but a slow reaction, whereas the acetonitrile can accelerate the reaction turnover with some sacrifice in enantioselectivity, it was only logical for us to investigate the bisolvent system. Thus the reactions were carried out in the DME/acetonitrile hybrid solvent system with a variation of solvent ratios (Table 3). To our delight, with **1a** as the substrate, an optimal DME/acetonitrile ratio of 4:1 was identified. Under this condition, the reaction could achieve 83% yield and 93% ee at room temperature for 56 h when 15 mol % $(DHQD)_2PHAL$ was used.

With this optimized reaction condition in hand, the scope of this trifluoromethylation protocol was investigated with a variety of MBH carbonates, and the results are summarized in Table 4. Substituents with

Table 3. Optimization of the DME−MeCN Bisolvent Ratio[a]

entry	ratio	time (h)	yield (%)	ee (%)
1	10:1	60	35	88
2	5:1	48	50	92
3	2:1	48	62	88
4	1:1	36	85	84
5[b]	4:1	56	83	93

[a] Reaction was carried out using **1a** (0.5 mmol), Me_3SiCF_3 (1.25 mmol), and $(DHQD)_2PHAL$ (0.05 mmol) in solvent (1.7 mL) at room temperature unless otherwise noted. [b] $(DHQD)_2PHAL$ (0.075 mmol) and solvent (1 mL) were used.

different electronic nature on the aromatic ring, such as nitro, methoxy, alkyl, alkene, and halogen, were tolerated (entries 1−6 and 9, Table 4; 32−86% yield, 87−94% ee). Generally, electron-withdrawing groups on the aromatic ring facilitated the reaction, whereas electron-donating substituents retarded the reaction. For substrates bearing electron-donating groups, the reaction could be modulated by increasing the amount of acetonitrile in the bisolvent system (entry 2, Table 4). Common protecting groups such as Ac, Boc, and allyl (entries 7 and 8; 47−80% yield, 58−94% ee) were also compatible in this system. Heteroaromatic ring systems such as furan, substituted furan, thiophene, thiazole, and quinoline were also viable replacements for the benzene ring in MBH substrates (entries 10−12, 14, and 15, Table 4; 54−84% yield, 48−92% ee). As expected, the electron-richer thiophene substrate provided product **2p** with lower yield and ee value than the product **2n** from 2-methyl thiazole substrate even under 1:1 DME/acetonitrile ratio . It should be noted that the styryl compound (entry 13, Table 4) gave exclusively allylic trifluoromethylated product **2m**[12] instead of a diene product, which might be generated via homoallylic trifluoromethylation of the active ionic intermediate. MBH substrates with alkyl substitution have also been examined (Scheme 2). However, when **1p** was used as the substrate and DABCO as the catalyst, the elimination process was predominant, likely resulted in intermediate **4a**. Dimerization of **4a** could further lead to the cyclized product **3p**, which was the solely isolated product with very high yield (93%). When sterically demanding cyclohexyl substrate **1q** was employed under the same reaction conditions, the elimination process was not observed, and the desired product **2q** was successfully isolated in 72% yield. However, the enantioselective trifluoromethylation of **1q** could not be achieved[13] even under long reaction time and higher temperature (5 days, 50 °C). This reaction is still under investigation.

(12) Structrue was assigned by COSY and HMBC. See Supporting Information.

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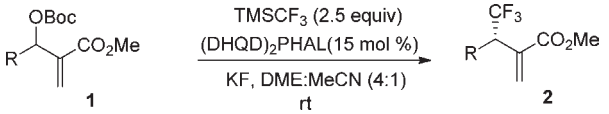
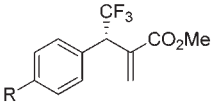
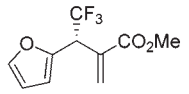
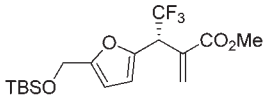
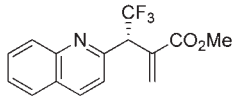
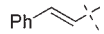
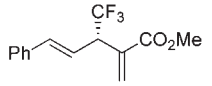
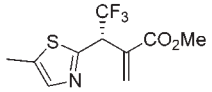
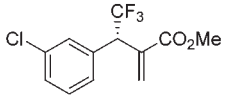
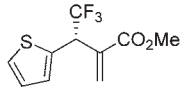
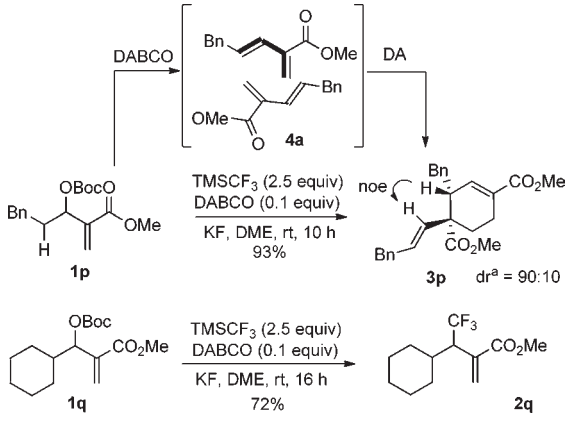
Table 4. Enatioselective Allylic Trimetylfluoromethylation of MBH Carbonates



entry	product[a]		time (h)	yield[b] (%)	ee[c] (%)	entry	product		time (h)	yield[b] (%)	ee[c] (%)
1		**2a**	56	83	93	10		**2j**	48	70	87
2[d]	R=OMe	**2b**	120	51	90	11[e]		**2k**	48	79	68
3	R=H	**2c**	60	72	94						
4	R= i-Pr	**2d**	120	32	87	12		**2l**	56	81	77
5	R= Cl	**2e**	60	70	93						
6	R= 	**2f**	72	86	92	13		**2m**	56	61	62
7	R= N(Boc)Ac	**2g**	120	47	58						
8	R= OAllyl	**2h**	110	80	94	14		**2n**	56	84	90
9		**2i**	60	69	94	15[d]		**2o**	120	54	48

[a] Sterochemistry was assigned by the chemical analogy of ref 8. [b] Isolated yield. [c] Enatiomeric excess was determined by chiral HPLC or SFC analysis. [d] Using DME/MeCN (1:1) as solvent. [e] Reaction was also performed in DME/MeCN (1:1) conditions; 80% yield and 67% ee were obtained.

Scheme 2. Reaction Using Alkyl-Substitued Substrates[a]



[a] Determined by ^{1}H NMR spectroscopy.

In summary, enantioselective allylic trifluoromethylation of Morita–Baylis–Hillman adducts using commercially available Ruppert reagent and a bis-cinchona alkaloid as catalyst has achieved good yield and excellent ee. The kinetic of this reaction was largely dependent on the electronic nature of the aromatic ring in the MBH substrates, with more electron-withdrawing groups providing facile reactions. Acetonitrile was also found to be able to accelerate the reaction rate, which allowed an efficient enantioselective synthesis of this class of compounds at room temperature.

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Supporting Information Available. Experimental procedures and compound characterization data including HPLC (SFC) data. This material is available free of charge via the Internet at http://pubs.acs.org.