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Enantioselective Synthesis of β-Trifluoromethyl-β-lactones via NHC-Catalyzed Ketene−Ketone Cycloaddition Reactions

Xiao-Na Wang, Pan-Lin Shao, Hui Lv, and Song Ye*

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

songye@iccas.ac.cn

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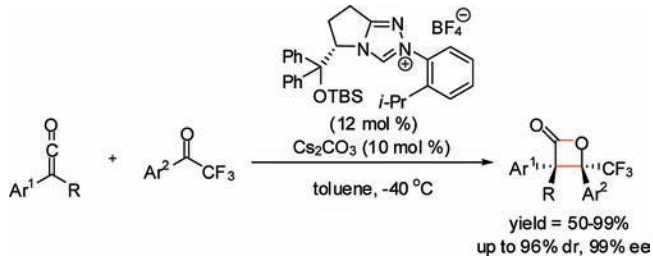
ABSTRACT



The highly diastereo- and enantioselective synthesis of β-trifluoromethyl-β-lactones bearing two contiguous stereocenters was realized by chiral N-heterocyclic carbene-catalyzed formal cycloaddition reaction of alkyl(aryl)ketenes and trifluoromethyl ketones.

Because of their unique properties, fluorinated compounds have found wide applications in pharmaceuticals, agrochemistry, and materials.[1] Among them, trifluoromethyl-substituted compounds are especially important and have been developed as several well-known drugs.[2] Thus, the efficient synthesis of these compounds has been pursued for decades.[3] In this context, commercially available trifluoromethyl ketones are valuable starting materials, and a wide variety of reactions, including aldol reaction, Friedal−Crafts reaction, alkynylation, alkenylation, arylation, and reduction, have been developed.[4]

β-Lactones not only are versatile building blocks in organic synthesis but also represent an important structural motif in many natural and unnatural bioactive compounds.[5,6] Although the synthesis of β-trifluoromethyl-β-lactones was patented in 1966,[7] to the best of our knowledge, the asymmetric synthesis of β-trifluoromethyl-β-lactones has not been realized.

N-Heterocyclic carbenes (NHCs) have been successfully demonstrated as catalysts for a variety of reactions,[8] including

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a^1-d^1 umpolung of aldehydes,[9] a^3-d^3 umpolung of α,β-unsaturated aldehydes,[10] umpolung of Michael acceptors,[11] aza-Mortia−Baylis−Hillman reaction,[12] and addition of silylated nucleophiles.[13] The synthesis of γ-trifuoromethyl γ-butyrolactones via NHC-catalyzed annulation of enals and ketones was reported by Glorius et al. and You et al.[14] Interestingly, Glorius et al. obsevered that, under certain reaction conditions, the corresponding β-lactones could be formed albeit in quite low yields and diastereoselectivities.[15]

Recently, the NHC-catalyzed enantioselective cycloaddition of ketenes and imines, 2-oxoaldehydes, enones, and *N*-benzoyldiazenes to give β-lactams, β-lactones, δ-lactones, and oxadiazinones, respectively, have been accomplished by Smith's and our group.[16] These findings prompted us to explore the asymmetric synthesis of β-trifluoromethyl-β-lactones via NHC-catalyzed ketene−ketone cycloaddition reactions.

Initially, a series of NHC precurors **4a**−**h** (Figure 1), derived from L-pyroglutamic acid,[16a] were tested for the [2 + 2]

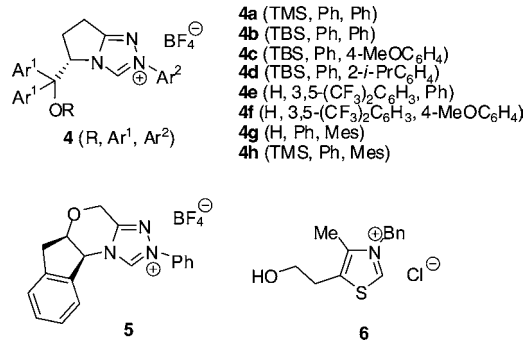
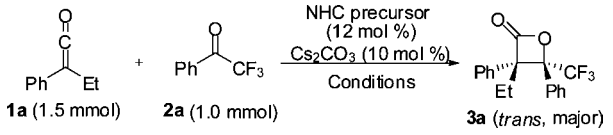


Figure 1. Structure of NHC precursors.

cycloaddition reaction of ethyl(phenyl)ketene (**1a**) and trifluoromethyl ketone **2a** (Table 1). It was found that NHC**4a′**,[17] generated freshly from its precursor **4a** and Cs_2CO_3,[18] could catalyze the reaction to give the corresponding β-trifluoromethyl-β-lactone **3a** bearing two contiguous stereocenters with good diastereoselectivity and enantioselectivity albeit in only 16% yield (entry 1). Better yield and enantioselectivity were observed when precatalyst **4b**, bearing a bulkier *tert*-butyldimethylsilyl group, was employed (entry 2). Further optimizations were carried out by installing an electron-donating group in the *N*-aryl group of the NHCs in order to increase the nucleophilicity of

Table 1. Optimization of Conditions for the NHC-Catalyzed Ketene−Ketone Cycloaddition Reaction[a]



entry	catalyst	conditions	yield (%)[b]	*trans*:*cis*[c]	ee (%)[d]
1	**4a**	toluene, rt	16	5:1	77
2	**4b**	toluene, rt	47	5:1	86
3	**4c**	toluene, rt	42	5:1	86
4	**4d**	toluene, rt	57	5:1	89
5	**4e**	toluene, rt	trace		
6	**4f**	toluene, rt	10	1:1	73
7	**4g**	toluene, rt	trace		
8	**4h**	toluene, rt	trace		
9	**5**	toluene, rt	trace		
10	**6**	toluene, rt	trace		
11	**4d**	benzene, rt	52	5:1	89
12	**4d**	ether, rt	43	4:1	88
13	**4d**	THF, rt	42	3:1	88
14	**4d**	CH_2Cl_2, rt	41	2:1	85
15	**4d**	toluene/ether (1:1), rt	50	4:1	87
16	**4d**	toluene, 0 °C	64	5:1	92
17	**4d**	toluene, −20 °C	65	6:1	96
18	**4d**	toluene, −40 °C	81	6:1	97
19	**4d**	toluene, −78 °C	NR		
20	**4d**[e]	toluene, −40 °C	71	6:1	97
21	**4d**[f]	toluene, −40 °C	17	6:1	97

[a] NHCs were prepared freshly from precursors **4**−**6** (12 mol %) in the presence of Cs_2CO_3 (10 mol %) at rt for 1 h. [b] Isolated yields. [c] Determined by ^{1}H NMR (300 MHz) and/or GC. [d] ee of *trans*-**3a**, determined by GC. [e] **4d** (6 mol %) and Cs_2CO_3 (5 mol %) were employed. [f] **4d** (1.2 mol %) and Cs_2CO_3 (1 mol %) were employed.

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(17) For convenience, the corresponding NHCs prepared from the precursors **4a**−**h** were denoted as NHCs **4a′**−**h′**.

(18) It was found that Cs_2CO_3 alone could promote the reaction. Thus a little excess of NHC precursor was used to make the full consumption of the base of Cs_2CO_3.

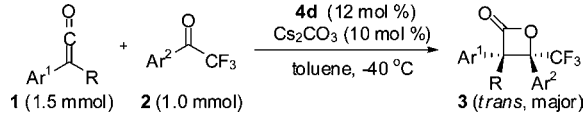
the corresponding NHCs.[19] Interestingly, although no notable difference was found for the reaction catalyzed by NHC**4c′** (Ar^2 = 4-$MeOC_6H_4$), NHC **4d′** (Ar^2 = 2-*i*-PrC_6H_4) resulted in better yield and enantioselectivity (entries 3 and 4). The NHCs **4e**−**g** bearing a free hydroxyl group showed very little activities for this reaction (entries 5−7).[20] NHC **4h**, which switched the enantioselectivities for the [4 + 2] cycloaddition reaction of ketenes with *N*-benzoydiazene in our previous report,[9e] did not work for this reaction (entry 8). Both the tetracyclic precatalyst **5** and thiazolium precatalyst **6** failed to catalyze the reaction under current reaction conditions (entries 9 and 10). Experiments revealed that toluene is the solvent of choice (entries 11−15) and −40 °C is the optimal reaction temperature (entries 16−19). Decreasing the loading of the NHC catalyst led to low yields but without notable change of diastereo- and enantioselectivities (entries 20 and 21).

A wide variety of aryl(alkyl)ketenes were then tested for the NHC-catalyzed reaction (Table 2). Both electron-donating and electron-withdrawing groups in aryl substituent of ketenes or in trifluoromethyl ketones are tolerable. Ketenes with methyl, ethyl, *n*-propyl, and *n*-butyl substituents all worked well. However, ketenes with a sterically bulky subsituent, such as 2-chlorophenyl and isopropyl, which worked well in the cycloaddition reaction with 2-oxoaldehydes,[9c] gave no β-lactones (entries 17 and 18). The reaction of benzyl(ethyl)ketene afforded the corresponding β-lactone in quantitative yield with 1:1 diastereoselectivity but excellent enantioselectivities for both diastereomers (entry 19).

A possible catalytic cycle is depicted in Figure 2. The stereochemical outcome of the cycloaddition reaction of ketenes and ketones catalyzed by NHC **4a′**−**d′** is the same as other reported [2 + 2] and [4 + 2] cycloaddition reactions of ketenes and imines, enones, and *N*-benzoylidiazenes catalyzed by NHC **4b′**. However, this stereochemical outcome is different from the formal cycloaddition of ketenes bearing bulkyl substituents and 2-oxoaldehydes.[16c,21]

In conclusion, chiral triazolium NHCs, derived from L-pyroglutamic acid, are found to be efficient catalysts for the enantioselective [2 + 2] cycloaddition reaction of aryl(alkyl)ketenes and trifluoromethyl ketones to give the corresponding β-trifluoromethyl-β-lactones bearing two contiguous stereocenters in high yields with good diastereoselectivities and excellent enantioselectivities.[22]

Table 2. Enantioselective Synthesis of β-Trifluoromethyl-β-lactones Catalyzed by NHC **4d′**



entry	**1** (Ar^1, R)	**2** (Ar^2)	**3**	yield (%)[a]	*trans*:*cis*[b]	ee (%)[c]
1	Ph, Et	Ph	**3a**	81	6:1	97
2	4-MeC_6H_4, Et	Ph	**3b**	86	7:1	95
3	4-$MeOC_6H_4$, Et	Ph	**3c**	90	7:1	93
4	4-ClC_6H_4, Et	Ph	**3d**	50	14:1	FD[d]
5	Ph, Me	Ph	**3e**	76	23:1	99
6	4-MeC_6H_4, Me	Ph	**3f**	84	17:1	99
7	Ph, Et,	4-ClC_6H_4	**3g**	89	9:1	98
8	4-MeC_6H_4, Et	4-ClC_6H_4	**3h**	93	11:1	99
9	4-$MeOC_6H_4$, Et	4-ClC_6H_4	**3i**	95	11:1	97
10	4-ClC_6H_4, Et	4-ClC_6H_4	**3j**	90	16:1	93
11	4-BrC_6H_4, Et	4-ClC_6H_4	**3k**	83	16:1	93
12	4-MeC_6H_4, Me	4-ClC_6H_4	**3l**[e]	96	12:1	99
13	Ph, *n*-Pr	4-ClC_6H_4	**3m**	99	4:1	FD
14[f,g]	Ph, *n*-Bu	4-ClC_6H_4	**3n**	81	6:1	FD
15[f]	Ph, Et	4-MeC_6H_4	**3o**	56	7:1	96
16[f]	4-MeC_6H_4, Et	4-MeC_6H_4	**3p**	60	7:1	FD
17	2-ClC_6H_4, Et	Ph		NR[h]		
18	4-ClC_6H_4, *i*-Pr	Ph		NR		
19	Bn, Et	4-$MeOC_6H_4$	**3q**	99	1:1	91

[a] Isolated yields. [b] Determined by ^{1}H NMR (300 MHz). [c] ee of *trans*-isomer, determined by GC (**3a**) and HPLC (**3b**−**q**). [d] FD = failed to determine the ee because the two enantiomers could not be separated on the Daicel chiralpak columns. [e] The absolution configurations of lactone **3l** was determined to be (3*S*,4*S*) by X-ray. [f] The ketenes were added in three portions every 3 h. [g] The reaction was carried out at room temperature. [h] NR = no reaction.

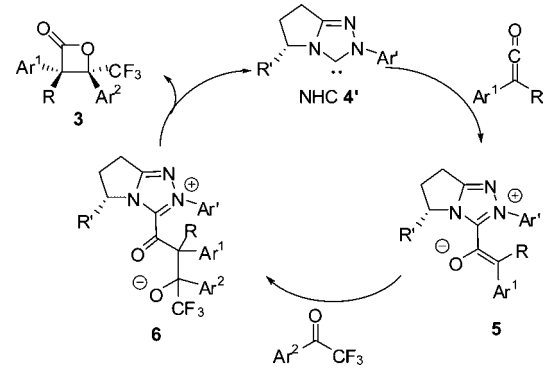


Figure 2. Proposed catalytic cycle.

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Supporting Information Available: Experimental procedures, compound characteriations, CD spectra, and crystal structure data of lactone **3l** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The different stereochemical outcome of bulky ketenes is also observed in the [4 + 2] cycloaddition reaction of ketenes with *N*-benzoyldiazenes (ref 16e).
(22) Attempts for the chemical transformations of β-lactone **3a** revealed that (1) compound **3a** was stable and did not decarboxylate upon heating in acidic conditions; (2) no reaction occurred under the saponification condition; and (3) reductive opening with $LiAlH_4$ led to a complex instead of the corresponding diol. See Supporting Information for details.