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Catalytic Asymmetric α-Aldol Reaction of Vinylogous *N*-Heterocyclic Carbene Enolates: Formation of Quaternary and Labile Tertiary Stereocenters

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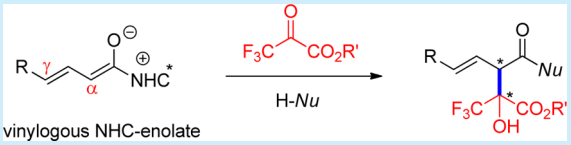
Supporting Information

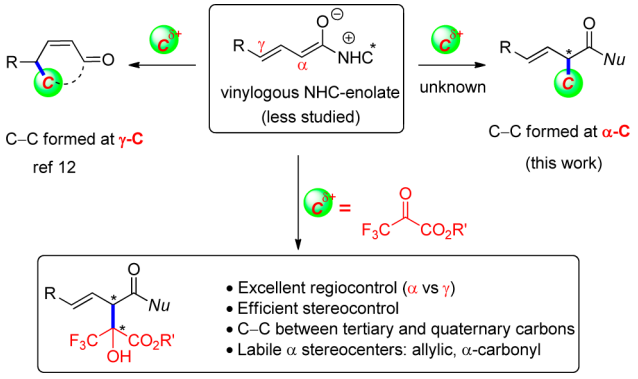
ABSTRACT: Simple *N*-heterocyclic carbene (NHC)-enolates are widely studied versatile species. However, their vinylogous siblings (i.e., vinylogous NHC-enolates) have been much less studied. Here we disclose the first catalytic asymmetric α-aldol reaction of vinylogous NHC-enolates. With trifluoropyruvate as the carbon electrophile, the efficient C−C bond formation process displays not only complete α-regioselectivity but also excellent stereocontrol over the two newly established challenging stereocenters (one quaternary and the other labile tertiary), furnishing a range of highly enantioenriched β,γ-unsaturated α-fluoroalkylated esters.



Asymmetric C−C bond formation is fundamentally important in organic chemistry.[1] In the past decade, organocatalytic C−C bond formation has seen exponential development, providing an attractive complement to the previously dominant metal- and biocatalytic approaches.[2] In particular, *N*-heterocyclic carbene (NHC) catalysis has emerged as a versatile platform for the discovery of new C−C bond-forming reactions.[3] Notably, these processes are typically highly enantioselective because of the excellent chiral transfer ability of the NHC-bound "umpolung" reagents, such as acyl anion equivalents, enolates, homoenolates, etc. Among them, NHC-enolates have received tremendous attention due to their versatility in reacting with various electrophiles to form α-chiral carboxylic acid derivatives, thus representing an attractive substitute to the traditional metal- and chiral auxiliary-based enolates.[4−9] However, in terms of C−C bond formation, the majority of these reactions are cycloaddition reactions (e.g., [4 + 2], [2 + 2], [2 + 2 + 2]).[10] Intermolecular asymmetric α-aldol-type reactions of NHC-enolates that do not involve ring formation are scarce.[11]

Furthermore, in contrast to the intensive studies of simple NHC-enolates, the reactivity of their vinylogous siblings (i.e., vinylogous NHC-enolates) have been much less studied,[12,13] despite the widely accepted importance of vinylogous enolates in remote C−C bond formation.[14] Ye and Chi pioneered the catalytic asymmetric C−C bond formation reactions of vinylogous NHC-enolates, but these reactions are again limited to cycloaddition at the γ position (Scheme 1).[12] To the best of our knowledge, C−C bond formation at the α position of vinylogous NHC-enolates is unknown. In continuation of our effort in NHC catalysis,[13a,15] here we report an efficient C−C bond formation that takes place not only selectively at the α position but also without cycloaddition. Specifically, considering the importance of fluoro- and trifluoromethyl-substituted molecules in medicinal chemistry and materials science,[16] we employed trifluoropyruvate as the carbon electrophile. Thus, the new C−C bond is formed between quaternary and labile tertiary (both allylic and α-carbonyl) stereocenters,[17] which is a challenge in terms of stereocontrol, particularly for acyclic products (Scheme 1).

Scheme 1. C−C Bond Formation of Vinylogous NHC-Enolates



We started the study with racemic γ-reducible enal **1a** as the model substrate to generate the vinylogous NHC enolate and methyl trifluoropyruvate **2a** as the carbon electrophile (Table 1). Due to the presence of a labile (racemizable) tertiary stereocenter in the desired product, the weak base K_2HPO_4 was employed. Initial evaluation of various NHC precatalysts with DCM as the solvent and MeOH as the nucleophile indicated that the desired product **3a** could be formed in low to moderate yield, but with good diastereoselectivity and excellent enantioselectivity (entries 1−6). Among them, triazolium salt

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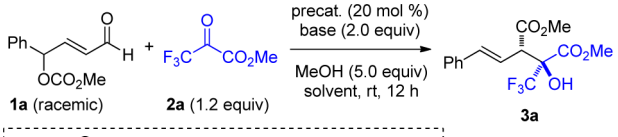
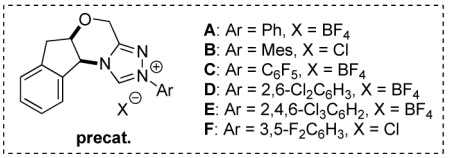
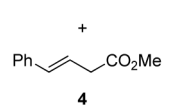
Table 1. Reaction Condition Optimization[a]







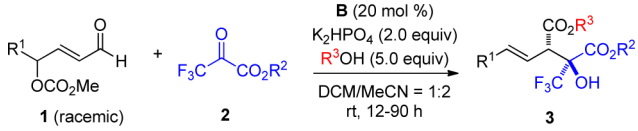
entry	precat.	base	solvent	yield (**3a**)[b]	dr (**3a**)[c]	ee (**3a**)[d]	**3a**/**4**[c]
1	**A**	K_2HPO_4	DCM	18%	15.0:1	96%	86:14
2	**B**	K_2HPO_4	DCM	57%	10.8:1	94%	84:16
3	**C**	K_2HPO_4	DCM	trace	–	–	–
4	**D**	K_2HPO_4	DCM	trace	–	–	–
5	**E**	K_2HPO_4	DCM	trace	–	–	–
6	**F**	K_2HPO_4	DCM	26%	6.0:1	90%	67:33
7	**B**	K_3PO_4	DCM	44%	8.3:1	93%	79:21
8	**B**	NaOAc	DCM	47%	8.5:1	92%	64:36
9	**B**	Cs_2CO_3	DCM	37%	1:1.2	83%	86:14
10	**B**	TEA	DCM	46%	5.5:1	77%	52:48
11	**B**	K_2HPO_4	*n*-hexane	29%	1.1:1	88%	53:47
12	**B**	K_2HPO_4	Et_2O	26%	5.0:1	87%	67:33
13	**B**	K_2HPO_4	MeCN	44%	3.3:1	93%	100:0
14	**B**	K_2HPO_4	EtOAc	43%	5.3:1	93%	84:16
15	**B**	K_2HPO_4	$MeNO_2$	18%	3.7:1	91%	58:42
16	**B**	K_2HPO_4	DCM/MeCN[e]	66%	9.5:1	96%	100:0
17[f]	**B**	K_2HPO_4	DCM/MeCN[e]	75%	9.1:1	96%	100:0

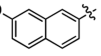
[a]The reaction was run with **1a** (0.05 mmol), **2a** (0.06 mmol), precat. (0.01 mmol), K_2HPO_4 (0.1 mmol), MeOH (0.25 mmol), and solvent (0.5 mL). [b]Combined yield of the diastereomers determined by ^{1}HNMR analysis of the crude reaction mixture with CH_2Br_2 as an internal standard. [c]The ratio (dr and **3a**/**4**) was determined by ^{1}HNMR analysis of the crude reaction mixture. [d]The ee value of the major diastereomer determined by HPLC analysis. [e]DCM/MeCN = 1:2 (v/v), 1.0 mL. [f]2.0 equiv of **2a**.

B gave the most promising results (entry 2).[18] Byproduct **4** was also observed, as a result of α-protonation instead of C−C bond formation of the corresponding vinylogous enolate. Next, various bases were screened. Other weak bases K_3PO_4 and NaOAc did not improve the product yield and diastereoselectivity. Relatively strong bases, such as Cs_2CO_3 and Et_3N, resulted in decreased stereoselectivity, presumably due to the base-labile α tertiary stereocenter. Subsequent solvent screening did not improve the results either (entries 11−15), but interestingly we found that the formation of byproduct **4** was suppressed with MeCN as solvent (entry 13). Inspired by this observation, we next resorted to mixed solvent using DCM and MeCN (v/v = 1:2), which slightly improved the product yield (entry 16). Finally, increasing the loading of **2a** resulted in the further enhanced yield of **4a** (75%) together with good diastereoselectivity and excellent enantioselectivity (entry 17).

With the optimized standard reaction conditions, next we carried out a scope study. As shown in Table 2, a wide range of γ aryl- and alkyl-substituted enals **1** could participate smoothly in the C−C bond formation process, and desired β,γ-unsaturated α-alkylated esters **3** were formed with good to excellent stereoselectivity. Ethyl trifluoropyruvate also provided similar levels of efficiency and selectivity (entries 14−19). Different alcohols, such as BnOH, allyl alcohol, and propargyl alcohol, could also serve as effective nucleophiles to form the corresponding ester products (entries 21−24). It is noteworthy

Table 2. Scope Study[a]



entry	R^1	R^2	R^3	time (h)	**3**	yield[b]	dr[c]	ee[d]
1	Ph	Me	Me	12	**3a**	82%	7.1:1	96%
2	2-MeC_6H_4	Me	Me	12	**3b**	74%	7.5:1	96%
3	2-$CF_3C_6H_4$	Me	Me	16	**3c**	46%	6.2:1	92%
4[e]	2-(vinyl)C_6H_4	Me	Me	90	**3d**	69%	10.3:1	97%
5	2-(TIPSOCH$_2$)C_6H_4	Me	Me	16	**3e**	78%	10.7:1	96%
6	3-(MeO)C_6H_4	Me	Me	12	**3f**	65%	6.2:1	96%
7[e]	3-$CF_3C_6H_4$	Me	Me	90	**3g**	56%	6.8:1	98%
8	3,5-$(CH_3)_2C_6H_3$	Me	Me	16	**3h**	73%	9.1:1	96%
9	4-MeC_6H_4	Me	Me	16	**3i**	71%	6.5:1	96%
10	4-(MeO)C_6H_4	Me	Me	12	**3j**	79%	6.6:1	96%
11	4-FC_6H_4	Me	Me	12	**3k**	64%	7.7:1	96%
12[e]	4-(vinyl)C_6H_4	Me	Me	90	**3l**	81%	9.5:1	98%
13		Me	Me	21	**3m**	63%	11.8:1	97%
14		Et	Me	22	**3n**	63%	11.8:1	95%
15	Ph	Et	Me	12	**3o**	80%	9.2:1	96%
16	2-MeC_6H_4	Et	Me	45	**3p**	72%	8.0:1	88%
17[e]	2-$CF_3C_6H_4$	Et	Me	90	**3q**	70%	4.5:1	94%
18[e]	3-(MeO)C_6H_4	Et	Me	90	**3r**	69%	8.0:1	98%
19[e]	4-FC_6H_4	Et	Me	90	**3s**	74%	7.0:1	98%
20	^{t}Bu	Me	Me	51	**3t**	55%	5.0:1	95%
21	Bn	Et	Bn	90	**3u**	41%	4.3:1	99%
22[e]	Ph	Me	Bn	40	**3v**	80%	4.7:1	99%
23[e]	Ph	Me	allyl	40	**3w**	79%	6.3:1	98%
24[e]	Ph	Me	propargyl	40	**3x**	81%	5.3:1	96%

[a]The reaction was run with **1** (0.35 mmol), **2** (0.70 mmol), **B** (0.07 mmol), K_2HPO_4 (0.7 mmol), R^3OH (1.75 mmol), and solvent (DCM/MeCN = 1:2, v/v, 7.0 mL). [b]Isolated combined yield of the diastereomers. [c]The dr value was determined by ^{1}H NMR of the crude mixture. [d]The ee value was determined by HPLC. [e]Run at 0 °C.

that in all these examples the C(sp^3)−C(sp^3) bonds between quaternary and labile tertiary stereocenters were all formed under mild conditions with excellent stereocontrol, which is particularly noteworthy for the formation of acyclic products.

In order to rationalize the absolute and relative stereochemistry of the two new stereocenters in the products, we have proposed conformation **I** for the vinylogous NHC-enolate and transition state **II** for the C−C formation step (Figure 1).

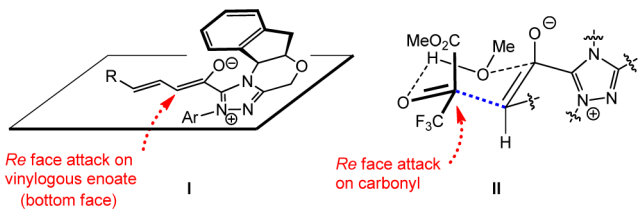


Figure 1. Plausible vinylogous NHC-enolate conformation and C−C bond formation transition state.

In conformation **I**, the chiral NHC backbone of the *Z*-enolate blocks the *Si* face and the electrophile approaches from the *Re* face (bottom face) for new bond formation, thus determining the absolute stereochemistry. In the C−C formation step, the orientation of the trifluoropyruvate determines the relative stereochemistry. We have proposed a six-membered chairlike transition state (**II**), in which a molecule of MeOH activates the electrophile carbonyl group through hydrogen bonding and simultaneously approaches the developing acyl carbon. In this

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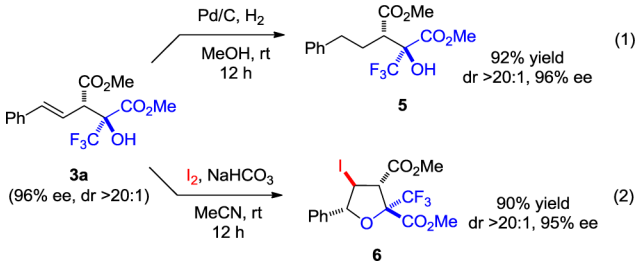
transition state, the large CF_3 group adopts the equatorial position (*A*-value of CF_3 2.4−2.5 > *A*-value of CO_2Me 1.2−1.3).[19] Thus, the enolate nucleophilic carbon attacks the *Re* face of the carbonyl, thereby setting the quaternary stereocenter. These rationalizations are in complete agreement with the observed product stereochemistry.

The highly enantioenriched products obtained via our catalytic intermolecular C−C bond-forming process can be transformed into other useful molecules. For example, the C═C bond in product **3a** can be efficiently hydrogenated to form saturated diester **5** without erosion in stereoselectivity (eq 1).



(1)

(2)

Moreover, due to the presence of a homoallylic alcohol subunit, product **3a** could undergo efficient iodoetherification in the presence of I_2 and $NaHCO_3$ to form densely functionalized tetrahydrofuran **6** as essentially a single diastereomer (eq 2). The relative stereochemistry was established by NOESY. It is worth noting that trifluoromethyl-substituted tetrahydrofuran subunits are of great interest in medicinal chemistry.[20]

In summary, we have disclosed an unprecedented intermolecular asymmetric α-aldol reaction of vinylogous NHC-enolates, a type of versatile but less explored species relative to simple NHC-enolates. In contrast to the known C−C bond formation at the γ position of vinylogous NHC-enolates, our reaction exhibits complete α selectivity. Unlike most cycloaddition reactions of NHC-enolates with external carbon electrophiles, our reaction does not involve a cycloaddition step. Notably, two challenging stereocenters, one quaternary and the other labile tertiary (both allylic and α-carbonyl), are also established in an acyclic product with excellent absolute and relative stereocontrol. A range of highly enantioenriched β,γ-unsaturated α-fluoroalkylated esters have been synthesized with high efficiency under mild conditions. These products can be easily transformed into other useful molecules, such as densely functionalized tetrahydrofurans. Further studies on vinylogous NHC-enolates are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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