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Enantioselective Diynylation of Cyclic *N*-Acyl Ketimines: Access to Chiral Trifluoromethylated Tertiary Carbinamines

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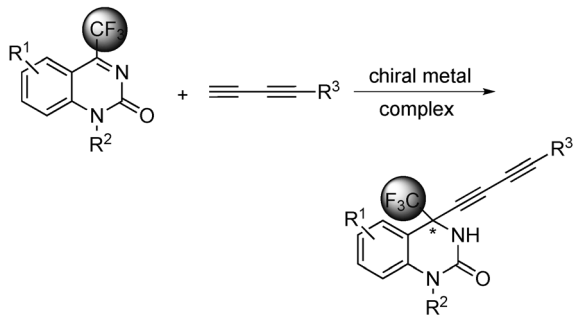
Abstract: A novel enantioselective diynylation of cyclic *N*-acyl trifluoromethylketimines with chloramphenicol-amine derivatives as chiral additives has been successfully developed. A series of diynylated tertiary trifluoromethylcarbinamines were obtained in high yields with good to excellent enantioselectivities (with up to 99% *ee*).

Keywords: addition reaction; asymmetric synthesis; chiral additives; enantioselectivity; ketimines

Chiral propargylic amines are important building blocks for the preparation of polyfunctional amino derivatives, pharmaceuticals, and biologically active compounds. Many synthetic methodologies have been developed to access these useful intermediates.[1] Among them, the metal-triggered direct asymmetric alkynylation of imines and analogues represents the most convergent and efficient approach to the synthesis of optically active propargylic amines. Over the past decade, a great effort has been devoted to the development of highly selective metal-promoted systems for these enantioselective alkynylation reactions.[2–7] Despite significant progress in this area, most studies are focused on the preparation of enantioenriched secondary carbinamines, and methods for the asymmetric synthesis of chiral tertiary carbinamines are very limited.[2,4a,e] Moreover, to date, there has been no attention paid to exploring terminal 1,3-diyne compounds as nucleophilic species in the enantioselective addition reaction of imines.

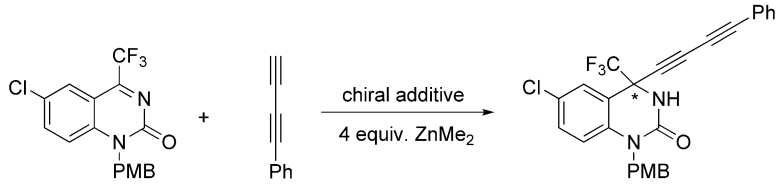
Diyne carbinamines, an important subset of propargylic amines, are useful building blocks for the synthesis of agrochemicals and compounds with potential biological activity.[8] However, the number of available methodologies for the preparation of diyne carbinamines remains scarce. They are mainly based on the oxidative coupling transformations involving terminal propargylic amines and propargylic alcohols.[9] Thus, the development of a direct asymmetric diynylation reaction of imines is highly desirable. Inspired by the recent pioneering work of Carreira,[10a] Trost,[10b] and Mikami[10c] on the metal-triggered asymmetric addition of diynes to aldehydes and ketones, we decided to develop a direct enantioselective addition of terminal 1,3-diynes to imines. Herein we report the results of our preliminary investigations on asymmetric diynylation of cyclic *N*-acyl trifluoromethylketimines, wherein chiral tertiary carbinamines were obtained with up to 99% *ee*. Owing to the unique properties of trifluoromethylated compounds, the asymmetric construction of chiral CF_3-containing molecules under mild conditions has become a highly desirable methodology in organic and medicinal chemistry.[11] This diynylation reaction provides a practical and operationally simple method for the installation of a trifluoromethyl group and a butadiyne moiety within a chiral molecule (Scheme 1).

In an initial investigation, the use of chiral Cu(I)-Pybox,[3a] Cu(I)-Quinap,[3c] and Cu(I)-Pinap[3e] com-



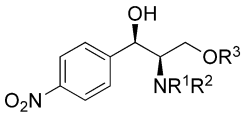
Scheme 1. Addition of diynes to cyclic *N*-acyl ketimines

Table 1. Screening of chiral additives and reaction conditions for the diynylation of ketimines.



1a **2a** **3a**

chiral additives:



I: $R^1 = R^2 = Me$, $R^3 = t$-Bu
II: $R^1 = R^2 = Me$, $R^3 = TBDMS$
III: $R^1 = R^2 = Me$, $R^3 = Tr$
IV: $R^1 = R^2 = -(CH_2)_4-$, $R^3 = Tr$
V: $R^1 = Me$, $R^2 = Bn$, $R^3 = Tr$
VI: $R^1 = Me$, $R^2 = 1\text{-}NapCH_2$, $R^3 = Tr$
VII: $R^1 = Me$, $R^2 = PMB$, $R^3 = Tr$
VIII: $R^1 = R^2 = PMB$, $R^3 = Tr$

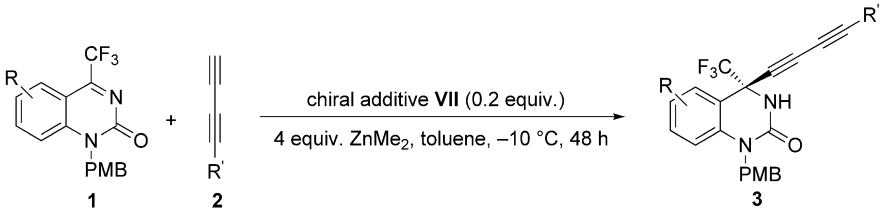
(TBDMS = *tert*-butyldimethylsilyl, Tr = triphenylmethyl, Bn = benzyl, Nap = naphthyl, PMB = *p*-methoxybenzyl)

Entry	Additive (equiv.)	Solvent	Temperature [°C]	Time [h]	Yield [%][a]	*ee* [%][b]
1	**I** (1)	toluene	25	12	99	46
2	**II** (1)	toluene	25	12	95	50
3	**III** (1)	toluene	25	12	99	77
4	**IV** (1)	toluene	25	12	97	55
5	**V**	toluene	25	12	99	90
6	**VI** (1)	toluene	25	12	97	71
7	**VII** (1)	toluene	25	12	99	91
8	**VIII** (1)	toluene	25	12	97	60
9	**VII** (1)	DCM	25	12	75	80
10	**VII** (1)	DCE	25	12	89	82
11	**VII** (1)	Et_2O	25	12	99	78
12	**VII** (1)	THF	25	12	12	70
13	**VII** (0.2)	toluene	25	12	97	91
14	**VII** (0.2)	toluene	0	48	97	92
15	**VII** (0.2)	toluene	−10	48	97	94
16	**VII** (0.1)	toluene	−10	48	90	90
17	**VII** (0.2)	toluene	−20	96	81	88
18[c]	**VII** (0.2)	toluene	−10	48	98	94

[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] The recovered diyne **2a** was used.

plexes in the addition of phenylbuta-1,3-diyne **2a** to cyclic *N*-acyl trifluoromethylketimine **1a** failed to afford the desired adduct, probably due to the attenuated nucleophilicity of hypercojugative 1,3-diynes compared to more reactive alkynes. Subsequently, we found that the addition of the *in situ*-generated diynylzinc species to ketimine **1a** proceeds well to produce the diynylation product **3a**. A series of chiral additives was then screened and the results are listed in Table 1. The use of chloramphenicol-amine derivative **I** quantitatively provided the adduct **3a**, but with only 46% *ee* (Table 1, entry 1). *tert*-Butyldimethylsilyl-substituted additive **II** gave similar results (entry 2). The enantioselectivity was increased to 77% when using triphenylmethyl-substituted compound **III** as an additive. After a systematic study of various substituents in the amino moiety of chloramphenicol-amine (entries 4–8, additives **IV**–**VIII**), we were pleased to find that the chiral additive **VII** affords the desired diynylation product **3a** in 99% yield with the best enantioselecitivity (91% *ee*). A comparison of the results obtained in different solvents showed that this enantioselective diynylation is highly sensitive to the solvent used (entries 9–12). Chloroalkanes and ethers generally gave lower *ee* values, and toluene was found to be the best solvent for this addition reaction. Decreasing the amount of chiral additive to 0.2 equivalents caused only a slight decrease in the yield (entry 13). Further optimization of the enantioselectivity of the process could be achieved with additive **VII** by lowering the reaction temperature (entries 14–17). Thus, the addition of diyne **2a** to cyclic *N*-acyl trifluoromethylketimine **1a** could be efficiently performed in toluene at −10 °C, delivering the adduct **3a** in 97% yield

Table 2. The scope of the addition of diynes to cyclic *N*-acyl ketimines.

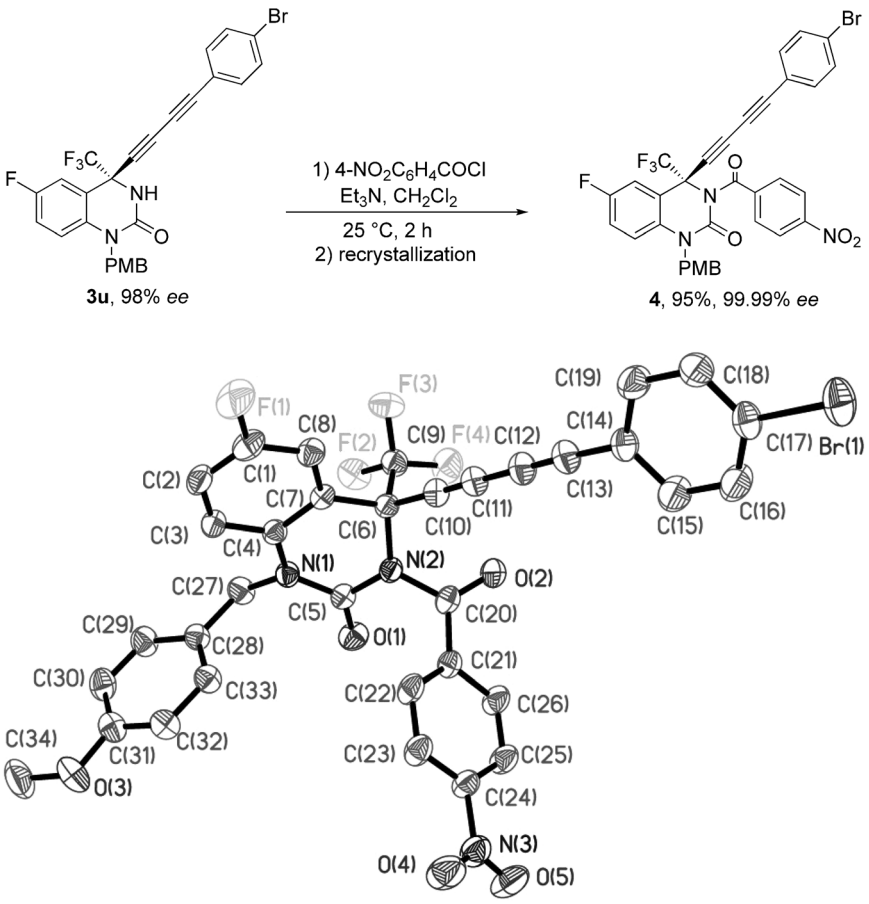


Entry		Product **3** (R; R′)	Yield [%][a]	*ee* [%][b]
1	**3a**	6-Cl; C_6H_5	97 (91)	94 (99)
2	**3b**	6-F; C_6H_5	92 (82)	91 (99)
3	**3c**	5-F, 6-Cl; C_6H_5	94 (70)	77 (97)
4	**3d**	6-MeO; C_6H_5	95 (88)	80 (93)
5	**3e**	6-Cl; 4-MeC_6H_4	97 (75)	76 (90)
6	**3f**	6-F, 4-MeC_6H_4	86 (70)	80 (97)
7	**3g**	6-Cl: 4-$MeOC_6H_4$	97 (90)	93 (99)
8	**3h**	6-F: 4-$MeOC_6H_4$	97 (88)	92 (97)
9	**3i**	5-F, 6-Cl; 4-$MeOC_6H_4$	98 (80)	83 (99)
10	**3j**	6-Cl; 2-$MeOC_6H_4$	97 (90)	90 (94)
11	**3k**	6-F; 2-$MeOC_6H_4$	97 (91)	94 (99)
12	**3l**	5-F, 6-Cl; 2-$MeOC_6H_4$	97 (82)	86 (99)
13	**3m**	5,6-F_2; 2-$MeOC_6H_4$	90 (77)	85 (95)
14	**3n**	6-Cl; 3-$MeOC_6H_4$	97 (79)	80 (96)
15	**3o**	6-F; 3-$MeOC_6H_4$	97 (80)	80 (94)
16	**3p**	6-Cl; 4-FC_6H_4	98 (80)	83 (99)
17	**3q**	6-F; 4-FC_6H_4	98 (93)	96 (97)
18	**3r**	6-Cl; 4-ClC_6H_4	97 (72)	75 (99)
19	**3s**	6-F; 4-ClC_6H_4	97 (80)	79 (96)
20	**3t**	6-Cl; 4-BrC_6H_4	93 (72)	78 (98)
21	**3u**	6-F; 4-BrC_6H_4	96 (82)	84 (98)
22	**3v**	6-Cl; 2-ClC_6H_4	97 (88)	91 (99)
23	**3w**	6-F; 2-ClC_6H_4	97 (90)	94 (99)
24	**3x**	6-Cl; 1-cyclohexenyl	97 (85)	85 (92)
25	**3y**	6-F; 1-cyclohexenyl	97 (90)	92 (95)
26[c]	**3z**	6-Cl; cyclopropyl	93 (77)	84 (97)
27[c]	**3a′**	6-F; cyclopropyl	93 (79)	85 (99)
28[c]	**3b′**	5,6-F_2; cyclopropyl	(50)	(97)
29	**3c′**	6-Cl; *n*-butyl	95	76
30	**3d′**	6-F; *n*-butyl	97	70

[a] Yield of isolated product.
[b] The *ee* value was determined by chiral HPLC analysis, and values in parentheses are for recrystallized products.
[c] The reaction was run at 0 °C.

with 94% *ee*. Although excess diyne is required for high reactivity and enantioselectivity, the unreacted diyne could be recovered and reused without any loss of reactivity and enantioselectivity (entry 18).

With the optimized reaction conditions in hand, the scope of the diynylation of cyclic *N*-acyl trifluoromethylketimines was explored by varying the terminal 1,3-diynes. The results are summarized in Table 2. Various aromatic diynes were studied by using (1*R*,2*R*)-**VII** as the additive. Electron-neutral, electron-withdrawing, and electron-donating groups as well as substrates substituted at different positions on the aromatic rings were good partners for the reaction. The desired products **3a**–**w** were obtained in 86–98% yields with 75–96% *ee* (entries 1–23). Alicyclic diynes also gave the diynylation adducts **3x**–**b′** in excellent yields with high enantioselectivities (entries 24–28). Linear alkyl-substituted 1,3-diynes are also viable substrates, affording the desired products in excellent yields, albeit with somewhat reduced enantioselectivity relative to the alicyclic partners (entries 29 and 30). All such products were isolated uniformly in the form of white solid powders. Noteworthily, in most cases an improvement of the enantiopurity of the adducts could be achieved by simple recrystallizaiton (entries 1–28). Although crystals suitable for X-ray diffraction analysis were not obtained for these diynylation adducts, further transformation

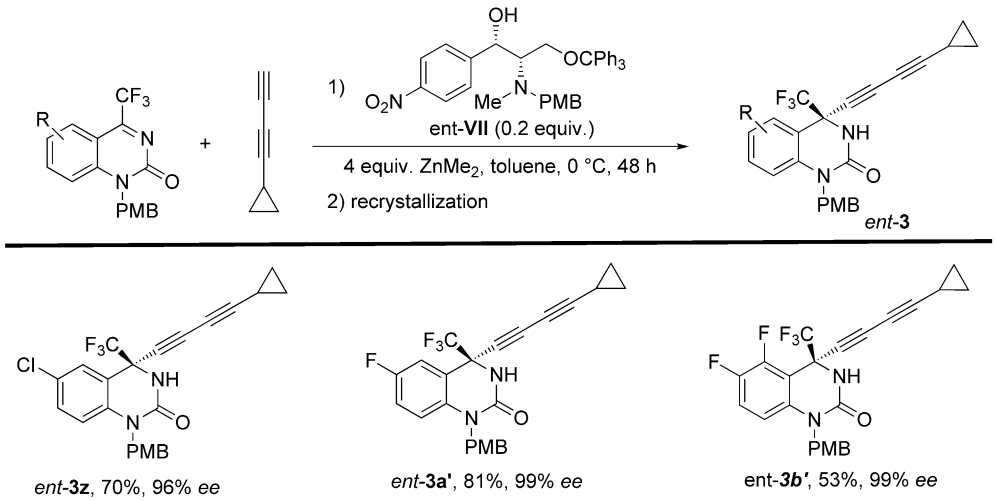


Scheme 2. Further transformation of product **3u** to **4** (*top*) and X-ray structure of **4** (*bottom*) for determination of the absolute configuration (Flack parameter 0.0009).

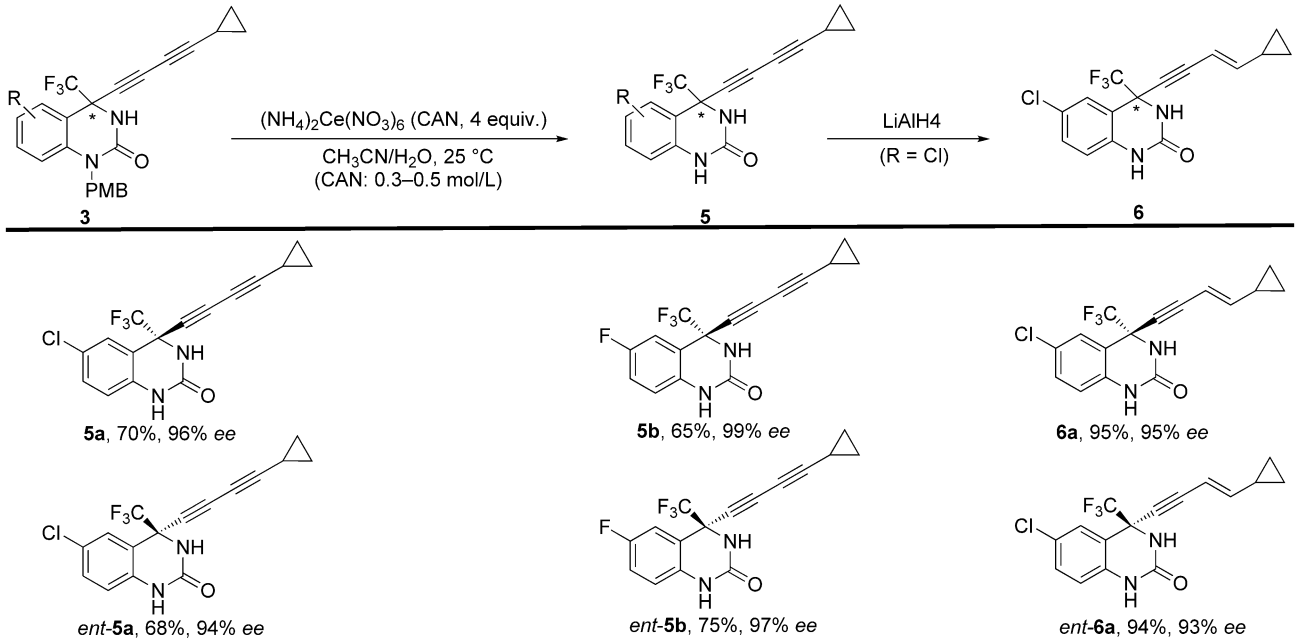
of the adduct **3u** furnished the crystalline derivative **4** whose absolute stereochemistry was determined from single-crystal X-ray structural analysis (Scheme 2).[12] Thus, we established that the absolute configuration of our diynylation products is *R*.

Studies on the scope of the reaction demonstrate the flexibility of the zinc-mediated asymmetric diynylation process to efficiently generate a range of new enantioenriched tertiary carbinamines. From both fundamental and practical standpoints, it is very important to provide methods to access both enantiomers. Hence, we prepared and characterized the additive *ent*-**VII**, which is derived from commercially available (1*S*,2*S*)-chloramphenicol-amine. This novel chiral additive allowed us to prepare the opposite enantiomers (*ent*-**3z**, *ent*-**3a′**, and *ent*-**3b′**) with excellent enantiopurity (Scheme 3). In addition, by removal of the *p*-methoxybenzyl (PMB) group in the adducts, and further reduction, the deprotected adducts can be readily transformed into functionalized amine derivatives. For example, treatment of the adducts (**3z**, **3a′**, *ent*-**3z**, and *ent*-**3a′**) with a solution of ceric ammonium nitrate (CAN) delivered the deprotected products **5** in 65–75% yields without any erosion of the enantiopurity (Scheme 4). Direct reduction of the adducts **5a** and *ent*-**5a** in the presence of $LiAlH_4$ gave (*E*)-eneynes **6a** and ent-**6a** in high yields with excellent enantiomeric purity.[2b] It is likely that the compounds prepared here will provide novel therapeutic agents and useful biological tools.

In conclusion, we have successfully developed a new and highly efficient procedure for the enantioselective addition of various terminal 1,3-diynes to cyclic *N*-acyl trifluoromethylketimines. A range of new trifluoromethylated tertiary carbinamines can be accessed in good to high yields (up to 98%) and enantioselectivities (up to 96% *ee*) from inexpensive and easily available chiral additives, and under mild conditions. Furthermore, higher enantiopurity of the adducts could be achieved by simple recrystallizaiton. These advantages make this procedure more suitable for practical use. In future studies we plan to investigate the biological activity of this intriguing class of trifluoromethylated tertiary carbinamines, and to expand the application of this diynylation addition to other substrates.



Scheme 3. *ent*-**VII**-mediated addition of cyclopropyl-substituted diyne to ketimines.



Scheme 4. Deprotection of the adducts **3** and further reduction to give the products **5** and **6**.

Experimental Section

General Procedure

A solution of Me_2Zn in toluene (1.2 M, 0.35 mL, 0.4 mmol) was added dropwise to the 1,3-diyne[10b] **2** (0.4 mmol) at room temperature under argon. The reaction mixture was stirred for 1 h, after which chloramphenicol-base derivative ligand **VII** (11.8 mg, 0.02 mmol) was added as a solid in one portion. After stirring for about 15–30 min, a solution of cyclic *N*-acylketimine **1** (0.1 mmol) in toluene (0.5 mL) was added by syringe, and the reaction mixture was stirred at under −10 °C until the reaction was complete (detected by TLC). The reaction mixture was quenched with 1 M aqueous HCl (5 mL), extracted with EtOAc (10 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) afforded the white solid powder **3** (unreacted equivalents of **2** could be recovered and reused). A simple recrystallization of this product from CH_2Cl_2/hexane gave the crystals with poor enantiopurity (*ee* < 20%), and the mother liquid was concentrated under reduced pressure to afford the desired product with high enantioselectivity (90–99% *ee*).

Acknowledgements

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[12] CCDC 830330 contains the supplementary crystallographic data for the compound **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.