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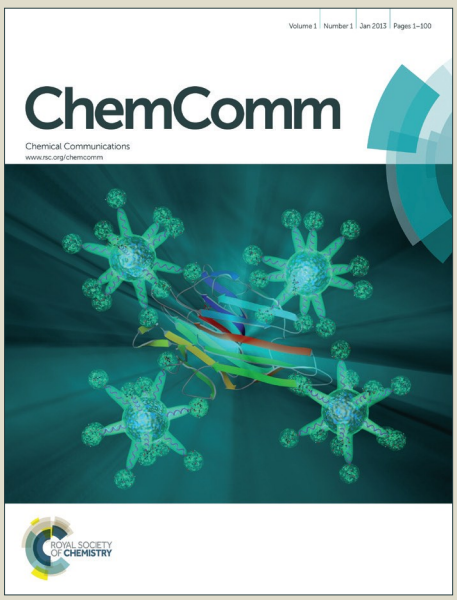

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An Efficient Approach to The Construction of Trifluoromethylated All-carbon Quaternary Stereocenters: Enantioselective Ni(II)-Catalyzed Michael Addition of 2-Acetyl Azaarene to β,β-Disubstituted Nitroalkenes

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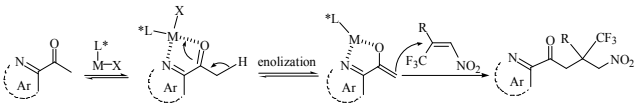
The first example of a highly enantioselective Michael addition of 2-acetyl azaarene with β, β-disubstituted nitroalkenes was achieved using a Ni(acac)$_2$-bisoxazoline complex as a catalyst, which afforded chiral compounds with an all-carbon quaternary stereocenter bearing CF_3 group in good yields with excellent enantioselectivities (up to >99% ee). The reaction, featuring mild condition, excellent enantioselectivity and broad generality, provides a new efficient strategy for the construction of trifluoromethylated all-carbon quaternary stereocenter.

The incorporation of trifluoromethyl group (CF_3) into organic molecular is able to improve efficiently chemical and metabolic stability, lipophilicity, and binding selectivity, resulting in unique bioactive properties. Thus trifluoromethyl group compounds are widelspread present in pharmaceutical, agrochemical products and materials.[1] As a result, the development of efficient and reliable methodologies for the introduction of trifluoromethyl groups into organic compounds has become one of the current hot-spots in fluorine chemistry. To date, a plenthora of methods have been developed for the synthesis of the trifluoromethyl group compounds.[2] Among them, the methods for the synthesis of optical CF_3-bearing compounds received rapidly increasing attention in recent years.[3] In particular, the development of efficient methods for the construction of all-carbon quaternary stereocenters bearing a CF_3-group is of great significance and very difficult area in organic synthesis. To our knowledge, only several examples of this type of reaction have been reported. In 2012 and 2013, Shibata *et al*. developed both highly enantioselective cyanation of β, β-CF_3 enones and conjugate addition of nitromethane to β, β-CF_3 enones to provide addition adducts bearing trifluoromethylated all-carbon quaternary stereocenters;[4] Gade *et al*. explored successfully a copper-catalyzed electrophilic trifluoromethylation of β-ketoesters.[5] Jia *et al*. demonstrated a highly enantioselective Ni-catalyzed Friedel–Crafts reaction of indoles with β, β-disubstituted nitroalkene to construct all-carbon quaternary stereocenters bearing CF_3 group.[6] Recently, Wang *et al.* realized an organocatalytic Michael-type reaction between oxindoles and trifluoromethylated nitroalkenes, affording oxindole compounds bearing a trifluoromethylated all-carbon quaternary stereocenter.[7]

In spite of these notable advances, the efficient method for the enantioselective construction of all-carbon quaternary stereocenter featuring a CF_3 group has been much limited and is still highly desirable.



Scheme 1 The strategy for Lewis acid-catalyzed Michael addition of 2-acetyl azaarene.

In Michael addition reaction, the Michael donor (nucleophile) is generally electron-rich arene, 1, 3-dicarbonyl or 1, 2-dicarbonyl compounds and other reagents plausible generating carbanion.[8] 2-Acyl azaarene, owing to its homology with 1, 2-dicarbonyl compounds in reaction pattern, is readily enolized upon treatment with Lewis acid, then can serve as a suitable nuecleophile in Michael addition. To the best of our knowledge, so far only one example involving 2-acyl azaarene in asymmetric Michael addition has been reported by Lam.[9] On the other hand, the above-mentioned β-CF_3-β-disubstituted nitroalkene is one versatile prochiral synthon for the synthesis of trifluoromethylated organic compounds, which remained to be further exploited in asymmetric catalysis.[10] As a result, we envisioned that the reaction of 2-acetyl azaarene with β-CF_3-β-disubstituted nitroalkene could proceed smoothly in the presence of appropriate Lewis acid catalyst, as shown in **Scheme 1**. Seeing from the previous reports on the construction of the all-carbon quaternary chiral center,[11] it is also a big challenge that overcoming the intrinsic steric hindrance and achieving excellent stereocontrol to generate the desired Michael adducts with a trifluoromethylated all-carbon quaternary stereocenter.

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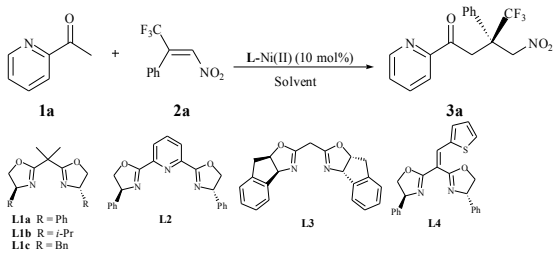
Table 1 Optimization of the reaction condition[a]



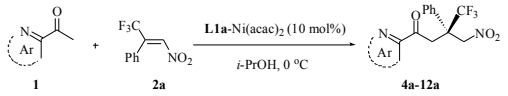
Entry	Ligand	Ni (II)	Solvent	T(°C)	Yield (%)[b]	Ee (%)[c]
1	**L1a**	$NiCl_2$	EtOH	25	n.d	-
2	**L1a**	$Ni(ClO_4)_2$	EtOH	25	n.d	-
3	**L1a**	$Ni(OAc)_2$	EtOH	25	43	89
4	**L1a**	$Ni(acac)_2$	EtOH	25	91	94
5	**L1b**	$Ni(acac)_2$	EtOH	25	88	80
6	**L1c**	$Ni(acac)_2$	EtOH	25	82	78
7	**L2**	$Ni(acac)_2$	EtOH	25	28	7
8	**L3**	$Ni(acac)_2$	EtOH	25	64	72
9	**L4**	$Ni(acac)_2$	EtOH	25	60	75
10	**L1a**	$Ni(acac)_2$	MeOH	25	91	95
11	**L1a**	$Ni(acac)_2$	*i*-PrOH	25	95	97
12	**L1a**	$Ni(acac)_2$	Et_2O	25	80	97
13	**L1a**	$Ni(acac)_2$	THF	25	35	95
14	**L1a**	$Ni(acac)_2$	DCM	25	60	94
15	**L1a**	**$Ni(acac)_2$**	**i-PrOH**	**0**	**95**	**99**
16[d]	**L1a**	$Ni(acac)_2$	i-PrOH	0	76	98
17[e]	**L1a**	$Ni(acac)_2$	i-PrOH	0	52	94

[a] All reactions were carried out in solvent (2mL) for 24h using 10 mol% Ni(II) and 11 mol% Ligand. [b] Isolated yields. [c] Determined by HPLC. [d] 5 mol% catalyst. [e] 2.5 mol% catalyst.

Gratifyingly, in our continuous efforts toward the development of new asymmetric reaction using simple and inexpensive catalytic system,[12] we recently found the first enantioselective Michael addition of 2-acetyl azaarene to β-CF_3-β-disubstituted nitroalkene using a chiral $Ni(acac)_2$-bisoxazoline complex, which provided the addition products with a trifluoromethylated all-carbon quaternary stereocenter in good yield and with high to excellent enantoselectivities (up to >99% ee). Herein we report our results on this subject.

The initial study was carried out by using 2-acetyl pyridine and β-CF_3-β-phenyl disubstituted nitroalkene as the model substrates in ethanol in the presence of chiral Ni(II) complex of ligand L**1a** (10 mol %) at room temperature. The results are listed in table 1. First, different Ni salts were screened. $Ni(acac)_2$ proved to be the optimal Ni source, giving the adduct **3a** in 91% yield and with 94% ee (Entries 1-4). Subsequently, Different chiral bisoxazoline ligands were examined. The reaction proceeded smoothly to afford the desired adducts in good yields for all tested ligands except for pybox **L2** (Entries 5−9). In terms of the enantitioselectivity and reactivity **L1a** was chosen as the optimal ligand (Entry 4). Moreover, a range of solvents such as methanol, *iso*-propanol, diethyl ether, THF and dichloromethane were tested, and afforded excellent enantioselectivities and different yields. Alcohols were superior to other solvents in reactivity, and particularly *iso*-propanol gave the best results (95% yield and 97% ee, entry 11). To our delight, lowering reaction temperature to 0°C made the enantioselectivity raise to 99% ee without any loss of reactivity (Entry 15). However, when the catalyst loading was reduced to 5mol% and 2.5mol%, the reaction became somewhat sluggishly, and proceeded for 24h at 0°C to afford a lower yield of product **3a**, meanwhile the enantioselectivity also dropped to some extent(Entries 16 and 17).

Table 2 The scope of 2-azaarenes[a]



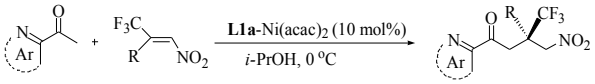
Entry	2-Azaaryl (**1**)	Product	T(h)	Yield (%)[b]	Ee (%)[c]
1	2-oxazolyl	**4a**	24	59	97
2	2-thiazolyl	**5a**	24	99	99
3	2-imidazolyl	**6a**	96	-	-
4	N-methyl-2-imidazolyl	**7a**	96	81	96
5	2-benzothiazolyl	**8a**	24	70	97
6	2-pyrazinyl	**9a**	96	92	99
7	2-pyrimidinyl	**10a**	120	67	85
8	2-quinolinyl	**11a**	120	71	97
9	2-oxazolyl	**12a**	96	72	97

[a]All reactions were carried out using $Ni(acac)_2$(10 mol%) and **L1a**(11 mol%) in *iso*-propanol (2mL) at 0°C under nitrogen. [b] Isolated yields. [c] Determined by HPLC.

Under the optimized reaction conditions (10 mol% **L1a**–$Ni(acac)_2$, *iso*-propanol as solvent and 0 °C), the generality of the reaction was next investigated by varying heterocycle moiety of 2-acetyl azaarene. The results are outlined in table 2. A variety of 2-acetyl azaarenes containing five-membered N-heterocycle demonstrated high to excellent enantioselectivities (96-99%ee, entries 1-5), although the reactivity was dramatically dependent on the structure of N-heterocycle. Among them, 2-acetyl thiazole was the most amenable substrate, affording the product **5a** in both 99% yield and 99% ee value. Surprisingly, 2-acetyl imidazole didn't take place (Entry 3), which presumably the intramolecular hydrogen bond between N-H and adjacent C=O bond hindered the reaction. This was also confirmed by the fact that, the reaction of N-methyl-2-acetyl imidazole proceeded smoothly to furnish the Michael adduct in 81% yield with 96% ee (Entry 4), Moreover the substrates containing six-membered N-heterocycle such as pyrazinyl, pyrimidinyl, quinolinyl and quinoxalinyl were well compatible with

the reaction. Although a longer reaction rime was needed for good yields, high to excellent enantiomeric excesses were achieved in the range of 85-99% (Entries 6-9).

Table 3 The scope of 2-nitroalkenes[a]

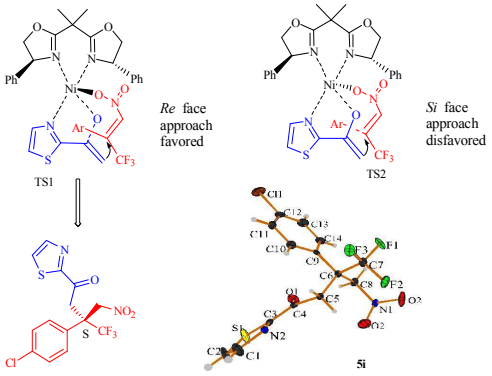


Entry	2-azaaryl	R	product	Yield (%)[b]	Ee (%)[c]
1	2-thiazolyl	*p*-MeC_6H_4	**5b**	97	99
2	2-thiazolyl	*p*-MeOC_6H_4	**5c**	81	99
3	2-thiazolyl	*m*-MeC_6H_4	**5d**	85	93
4	2-thiazolyl	*m*-MeOC_6H_4	**5e**	91	99
5	2-thiazolyl	*o*-MeC_6H_4	**5f**	-	-
6	2-thiazolyl	*o*-MeOC_6H_4	**5g**	-	-
7	2-thiazolyl	*p*-FC_6H_4	**5h**	71	97
8	2-thiazolyl	*p*-ClC_6H_4	**5i**	86	94
9	2-thiazolyl	*p*-F_3CC_6H_4	**5j**	80	98
10	2-thiazolyl	*m*-FC_6H_4	**5k**	76	99
11	2-thiazolyl	*m*-ClC_6H_4	**5l**	65	>99
12	2-thiazolyl	*m*-$CF_3C_6H_4$	**5m**	79	98
13	2-thiazolyl	biphenyl	**5n**	62	99
14	2-thiazolyl	3-thienyl	**5o**	73	93
15	2-thiazolyl	cyclohexyl	**5p**	72	99
16	2-thiazolyl	*n*-octanyl	**5q**	79	96
17	2-pyridinyl	*p*-MeC_6H_4	**3b**	94	97
18	2-pyridinyl	*p*-MeOC_6H_4	**3c**	95	96
19	2-pyridinyl	*p*-ClC_6H_4	**3d**	93	91
20	2-pyridinyl	*p*-F_3CC_6H_4	**3e**	86	94
21	2-pyrazinyl	*p*-MeOC_6H_4	**9a**	78	99
22	2-pyrazinyl	*p*-F_3CC_6H_4	**9b**	90	98

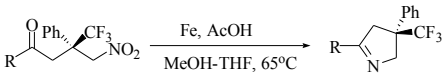
[a]All reactions were carried out using using Ni(acac)$_2$(10 mol %) and **L1a**(11 mol %) in *i*-propanol (2mL) at 0°C under nitrogen. [b] Isolated yields. [c] Determined by HPLC.

fter investigating 2-acetyl azaarenes, we next evaluated the scope of nitroalkenes. The results are summarized in table 3. First, 2-acetyl thiazole, owing to its affording excellent enantioselectivity and reactivity, was selected to react with various β-CF_3 nitroalkenes. Having an electron-rich or electron-deficient substituent at the *para*- or *meta*- position of phenyl ring, the reaction occurred smoothly to afford the adducts **5b~5m** in good yield with excellent enantioselectivities (94->99% ee, entries 1-12). These results exhibited the electronic property of the substituent on the phenyl ring of nitroalkene has little influence on the enantioselectivity and reactivity of the reaction. However the *ortho*-substituent on the phenyl ring of nitroalkene has a remarkable negative influence on the reaction. No reaction took place with substrate bearing an *ortho*-methyl or -methoxy on the phenyl ring, which is probably attributed to the bulky steric hindrance at *ortho*-position of phenyl ring (Entries 5 and 6). Moreover substrates bearing a biphenyl or thienyl group also achieved the same good results (Entries 13 and 14). It was worth noting that the reaction could be successfully extended to alkylated substrates. Excellent enantiomeric excesses were obtained for substrates with a cyclohexyl or octanyl group (99% and 96% ee, respectively, entries 15 and 16). Furthermore, when heterocycle moiety of 2-azaarene was changed from thiazole to pyridine or pyrazine, the reactions with nitroalkenes bearing different substituted phenyl group also worked well to afford the Michael products in excellent enantioselectivities (91-99% ee, entries 17-22). It is noteworthy that multifluorinated products (**5j**, **5m**, **3e** and **9b**) were readily achieved in good yields and with excellent ee values.

The absolute configuration of the product **5h** was determined to be *S* on the basis of its single-crystal X-ray structure.[13] A possible transition state was proposed to account for the observed enantioselectivity, as shown in **Scheme 2**. First, the coordination of BOX ligand to Ni(acac)$_2$ give rise to a chiral Lewis acid catalyst (Ni complex), which subsequently interact with 2-acetyl azaarene to result in the Ni enolate. It is an important factor in influencing the enantioselectivity and reactivity that nitroalkene was also activated by the coordination of nitro group to chiral Ni(II) complex. Finally, the activated enolate preferably approaches the E-configured nitroalkene from the *Re* face(TS1), leading to the formation of the predominant *S*-configured product **5i**. If the enolate approaches the *E*-configured nitroalkene from the *Si* face, the corresponding transition state TS2 would be introduced, in which the steric hindrance between the phenyl group of ligand **L1a** and nitroalkene could make it unstable and disfavored. This catalytic process can be also regarded as "catalytic double activation method(CDAM)", in which both substrates are activated by Lewis acid, therefore subsequent Michael addition become easily.[14] In this asymmetric transformation nitro group and CF_3-group are essential for achieving high enantioselectivity and good reactivity. When using CN or CO_2Et group instead of NO_2 group in nitroalkene the reaction didn't occur; when the CF_3 group was replaced by a CH_3 group the reaction also ceased.



Scheme 2 Plausible transition state model.



3a, R = 2-Py **13a** R = 2-py, 66% yield, 98% ee
5a, R = 2-thienyl **13b** R = 2-thienyl, 80% yield, 99% ee

Scheme 3 One-pot synthesis of pyrroline derivatives.

To demonstrate the synthetic potential of this catalytic approach, the product **3a** and **5a** were subjected to one-pot reaction with three-step sequence (nitro reduction/intramolecular nucleophilic addition/dehydration cyclization) using Fe/AcOH in a mixed solvent of THF-MeOH, and provided pyrroline derivatives **13a** and **13b** in good yield without any loss in the enantiopurity (98% and 99% ee, respectively), as shown in **Scheme 3.** Compound **13** could serve as the key intermediate for the synthesis of the potential agrochemicals.[4b]

In summary, we have developed an efficient asymmetric Michael addition of 2-acetyl azaarenes to various β-CF_3-β-disubstituted nitroalkenes using a Ni(II)-bisoxazoline complex. The reaction can proceed at 0°C to afford the corresponding addition adducts bearing a trifluoromethyl all-carbon quarternary chiral center which are potentially useful intermediates in the synthesis of versatile optically enriched molecules. This method, featuring mild condition, high enantioselectivity and broad substrate scope, provides a new efficient strategy for the construction of trifluoromethylated all-carbon quaternary stereocenters.

Acknowledgements

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