Heterocycle Synthesis

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Efficient Access to Trifluoromethyl Diarylpyrrolines and their N-Oxides through Enantioselective Conjugate Addition of Nitromethane to β,β-Disubstituted Enones**

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Control of a hydrogen-bonding network between catalysts and substrates is one of the most important factors for the success of organocatalytic enantioselective reactions.[1] In 2010, we reported the first catalytic asymmetric synthesis of the 5-trifluoromethyl-2-isoxazolines **1**, which can be used as veterinary medicines, from the sterically demanding β-aryl-β-trifluoromethyl aryl-enones **2** using chiral ammonium salts of 9-OH cinchona alkaloids (**4**, type A) through a conjugate addition/cyclization/dehydration sequence (Figure 1).[2] We next succeeded in the catalytic, asymmetric synthesis of the β-

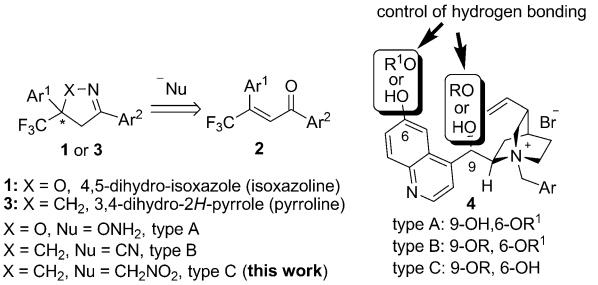

Figure 1. Strategies for asymmetric synthesis of the trifluoromethylated 2-isoxazolines **1** and pyrrolines **3** from the β-aryl-β-trifluoromethyl aryl enones **2** using cinchona alkaloids catalysis.

trifluoromethyl 3,5-diaryl-pyrrolines **3** ($X = CH_2$) by enantioselective conjugate addition of cyanide to **2**.[3] In this process, the 9-OH-protected cinchona alkaloids **4** (type B) are effective in achieving a high level of enantioselectivity. We report herein the high-yielding asymmetric synthesis of **3** by the conjugate addition of nitromethane to **2**, using the cinchona alkaloids **4** of type C (with 6-OH and protected 9-OH groups), as a key step.

Trifluoromethylated 3,5-diaryl-pyrrolines (**3**) were developed as carbon variants of **1**, and have attracted much attention because of their promising agrochemical activity, including use as an antiparasitic.[4] Since their initial discovery in 2005,[4a] more than 7000 racemic mixtures of **3** have been registered in SciFinder, and most of them have been protected by patents.[5] In 2012, we disclosed the first enantioselective methodology for the synthesis of **3** by means of cinchona-alkaloid-catalyzed enantioselective conjugate cyanide addition to β-aryl-β-trifluoromethyl aryl-enones **2**, and a subsequent cyano reduction/cyclization/dehydration sequence mediated by Raney nickel.[3] Despite the high enantioselectivities observed in the first conjugate addition step, the cyano reduction step requires a harsh Raney nickel treatment, thus resulting in moderate yields (around 50%) of **3**. Additionally, it is difficult for the halogen group on aromatic rings to survive the Raney nickel treatment. These aspects are critical drawbacks of agrochemical synthesis since the fundamental structure of **3** contains a 3,5-dichlorophenyl moiety at the 5-position of the pyrroline ring, thus another strategy is required. We disclose herein an efficient asymmetric synthesis of **3** by the enantioselective conjugate addition of nitromethane to **2** catalyzed by ether-type cupreidinium salts. The success of this enantioselective conjugate addition results from hydrogen-bonding system. We also attempted the asymmetric synthesis of active pesticidal *N*-oxide variants of **3**,[4b,i,6] which are polar isosteres of **3**.

It was necessary to develop an enantioselective conjugate addition of nitroalkanes to **2** for this purpose. Although numerous papers have appeared on the enantioselective conjugate addition of nitroalkanes to β-monosubstituted α,β-unsaturated carbonyl compounds,[7] examples of enantioselective conjugate addition to β,β-disubstituted substrates are very rare and remain one of the challenges in organic chemistry.[8] Recently, Kudo et al. reported the peptide-catalyzed asymmetric conjugate addition of nitromethane to β,β-disubstituted-α,β-unsaturated aldehydes.[8d] However, this iminium activation strategy requires an aldehyde function on the substrates, hence it is not applicable to β,β-disubstituted enones. In 2012, we reported an enantioselective conjugate addition of nitromethane to a β-monosubstituted trifluoromethylated enone catalyzed by cinchona alkaloid/thiourea derivatives.[9] We then applied the method to a β,β-disubstituted enone, (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one (**2a**). Trace amounts of the product **5a** were obtained even after one week of stirring, despite observing high enantioselectivity (Scheme 1).

Since we experienced difficulties in improving the conversion of this process after many attempts,[10] we switched from a thiourea type catalysis to a phase-transfer catalytic

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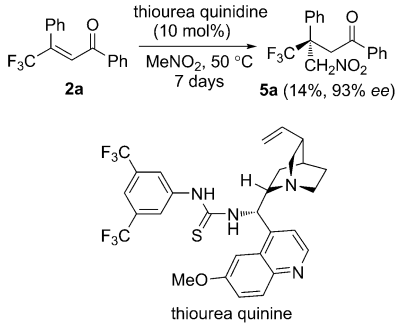
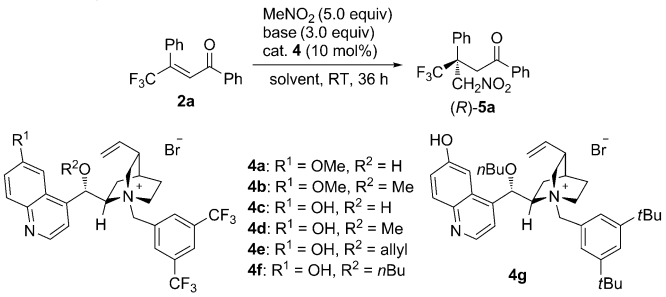


Scheme 1. The conjugate addition of nitromethane to **2a** using cinchona alkaloid/thiourea catalyst.

mode (Table 1). We first attempted the reaction in the presence of K_2CO_3 in toluene using the quinidine-derived catalyst **4a**, which is the best catalyst for the hydroxylamine enone cascade reaction to **2**.[2] Contrary to our expectations, **5a** was isolated in low yield with 17% *ee* (entry 1). We next used **4b**, which is effective for the enantioselective conjugate cyanation of **2**.[3] However, the observed enantioselectivity was low (entry 2). This led us to change the catalyst character entirely. It is reported that the hydroxy group of cinchona alkaloids often plays an important role both in reactivity and in asymmetric induction, probably by hydrogen bonding with substrates.[11] Therefore, we focused on the cupreidine-based phase-transfer catalyst, since they have a different mode of hydrogen bonding to substrates.[12] Gratifyingly, an improved *ee* value of 57% was observed in the presence of **4c** (entry 3). When the reaction was carried out using the methylether cupreidinium salt **4d**, the desired **5a** was obtained in 49% with 85% *ee* (entry 4). This promising result spurred us to investigate the protection of the 9-OH group (see Table S1 in the Supporting Information). Enantioselectivity was slightly improved to 86% *ee* using the *n*-butylether cupreidinium salt **4f** (entry 6). The sterically demanding cupreidinium derivative **4g** also proved to be an almost equally effective catalyst, thus affording **5a** in 52% yield with 86% *ee* (entry 7). Rb_2CO_3, Cs_2CO_3, and K_3PO_4 showed higher reactivities, but enantioselectivities were lower than those obtained with K_2CO_3 (entries 8–11). A subsequent solvent survey (entries 12–20) revealed that benzene was the solvent of choice with regard to enantioselectivity (entry 15). Further improvement of selectivity was observed in the presence of 4 Å M.S. (50 mg) to give **5a** with 92% *ee* (entry 21). The amount of 4 Å M.S. affects the yield significantly, and we found that a reduced amount (10 mg) led to higher reactivity while maintaining high enantioselectivity (entry 23). The use of **4g** under the same reaction conditions gave a slightly better result (entry 24). When we attempted the reaction at 35 °C, improved chemical yield was obtained while maintaining the same level of enantioselectivity (entry 25). Catalyst loading is important for the reaction rate. Indeed, the use of 20 mol% of **4g** gave a higher chemical yield with 92% *ee* (entry 27).

With optimal reaction conditions in hand, the scope of the enantioselective conjugate addition of nitromethane with a variety of β-aryl-β-trifluoromethyl-substituted enones (**2**) in the presence of a catalytic amount of **4g** was explored in to establish the generality of the process, all affording excellent yields and enantioselectivities (Table 2). A series of trifluoromethylated enone derivatives (**2a–g**, **2i–o**) with a variety of substituents, such as methyl, methoxy, fluoro, chloro, bromo, and nitro groups, on their aromatic rings were converted into the corresponding **5a–g**, **i–o** in high to excellent yields with *ee* values in the range of 90–93% (entries 1–7, 9–15). The sterically demanding naphthyl-substituted enones **2h** and **2p** also reacted, thus affording **5h** and **5p**, respectively, in excellent yields with 90% *ee* (entries 8 and 16). Notably, the multiply substituted substrate **2q** was also smoothly converted into the desired 1,4-adduct **5q** with 91% *ee* (entry 17).[13] Although an aromatic group (R = Ar) is indis-

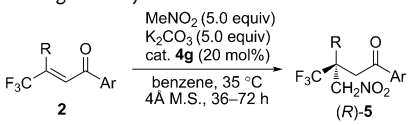
Table 1: Optimization of reaction conditions.[a]



Entry	Base	Solvent	4	Yield [%][b]	*ee* [%][c]
1	K_2CO_3	toluene	**4a**	28	17 (*S*)
2	K_2CO_3	toluene	**4b**	62	10
3	K_2CO_3	toluene	**4c**	10	57
4	K_2CO_3	toluene	**4d**	49	85
5	K_2CO_3	toluene	**4e**	48	82
6	K_2CO_3	toluene	**4f**	50	86
7	K_2CO_3	toluene	**4g**	52	86
8	Rb_2CO_3	toluene	**4f**	82	53
9	Cs_2CO_3	toluene	**4f**	96	53
10	K_3PO_4	toluene	**4f**	73	59
11	KOH	toluene	**4f**	trace	n.d.
12	K_2CO_3	*o*-xylene	**4f**	55	83
13	K_2CO_3	*m*-xylene	**4f**	48	82
14	K_2CO_3	mesitylene	**4f**	49	78
15	K_2CO_3	benzene	**4f**	50	88
16	K_2CO_3	CH_2Cl_2	**4f**	31	82
17	K_2CO_3	$CHCl_3$	**4f**	32	83
18	K_2CO_3	THF	**4f**	56	45
19	K_2CO_3	iPr_2O	**4f**	41	67
20	K_2CO_3	$MeNO_2$	**4f**	90	21
21[d]	K_2CO_3	benzene	**4f**	21	92
22[e]	K_2CO_3	benzene	**4f**	37	92
23[f]	K_2CO_3	benzene	**4f**	46	92
24[f]	K_2CO_3	benzene	**4g**	44	93
25[f,g]	K_2CO_3	benzene	**4g**	61	92
26[f,g,h]	K_2CO_3	benzene	**4g**	67	92
27[f,g,h,i]	K_2CO_3	benzene	**4g**	90	92

[a] The reaction of **2a** with $MeNO_2$ (5.0 equiv) was carried out in the presence of **4** (10 mol%) and base (3.0 equiv) in solvent (0.5 mL, 0.2 M) at room temperature, unless otherwise noted. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Used 50 mg of 4 Å M.S. [e] Used 20 mg of 4 Å M.S. [f] Used 10 mg of 4 Å M.S. [g] The reaction was carried out at 35 °C. [h] Used 5.0 equiv of base. [i] Used 20 mol% of catalyst **4**. M.S. = molecular sieves, n.d. = not determined, THF = tetrahydrofuran.

Table 2: Substrate generality.[a]



Entry	2	R	Ar	5	Yield [%][b]	*ee* [%][c]
1	**2a**	Ph	Ph	**5a**	90	92
2	**2b**	3-MeC_6H_4	Ph	**5b**	91	91
3	**2c**	4-MeC_6H_4	Ph	**5c**	99	92
4[d]	**2d**	4-$MeOC_6H_4$	Ph	**5d**	92	90
5	**2e**	4-FC_6H_4	Ph	**5e**	80	91
6	**2f**	4-ClC_6H_4	Ph	**5f**	85	90
7[e]	**2g**	4-BrC_6H_4	Ph	**5g**	86	91
8[e,f]	**2h**	2-naphthyl	Ph	**5h**	92	90
9	**2i**	Ph	3-MeC_6H_4	**5i**	91	91
10	**2j**	Ph	4-MeC_6H_4	**5j**	90	93
11[d]	**2k**	Ph	4-$MeOC_6H_4$	**5k**	87	90
12	**2l**	Ph	4-FC_6H_4	**5l**	90	90
13	**2m**	Ph	4-ClC_6H_4	**5m**	94	92
14	**2n**	Ph	4-BrC_6H_4	**5n**	99	92
15[e,g]	**2o**	Ph	4-$NO_2C_6H_4$	**5o**	86	93
16	**2p**	Ph	2-naphthyl	**5p**	92	90
17[e,g,h]	**2q**	3,5-$Cl_2C_6H_3$	3-Me-4-BrC_6H_3	**5q**	80	91
18[e,g,i]	**2r**	Me	Ph	**5r**	90	63

[a] The reaction of **2** with $MeNO_2$ (5.0 equiv) was carried out in the presence of **4g** (20 mol%) and K_2CO_3 (5.0 equiv) in benzene (0.5 mL, 0.2 M) at 35 °C, unless otherwise noted. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The reaction was carried out at 50 °C. [e] The reaction was carried out at ambient temperature. [f] Used 30 mol% of **4g**. [g] The concentration was 0.04 M. [h] Used 10.0 equiv of $MeNO_2$. [i] The absolute configuration of **5r** is not determined.

pensable for potent biological activity of **3**, we briefly attempted the enantioselective conjugate addition of nitromethane to the alkyl-substituted enone **2r** (R = Me) to investigate the potential of this reaction. Interestingly, the alkyl substituent at the β-position was also tolerated and a rather high level of enantiodiscrimination was observed for the **4g**-catalyzed conjugate addition to provide **5r** in 90% with 63% *ee*, despite the somewhat small steric difference between CH_3 and CF_3 on the β-position of **2r** (entry 18).

Based on our previous speculation[2] on the reaction mechanism involving charge-accelerated catalysis using a rigid quaternary ammonium salt,[14] as established by the X-ray crystallographic structure of related cinchona alkaloids[2,12b,15] and molecular calculation of **2a**,[2] we postulated a transition-state structure for the production of (*R*)-**5** catalyzed by **4g** and the nitromethane anion (Figure 2). The free hydroxy group in **4g** engages in an intermolecular hydrogen-bond formation with the oxygen atom in **2a**. Only the arrangement shown in Figure 2 could be plausible because of the limited space made available by the sterically demanding and rigid structure of **4g**. The nitromethane anion generated by the base is located as a nearest neighbor by ion pairing with the nitrogen cation of **4g**. The nitromethane approaches from the *Re* face of **2a**. Both the hydrogen bonding between prochiral substrate **2a** and **4g**, and the ionic interaction between **4g** and the nitromethane anion should result in the highly enantioselective reaction.

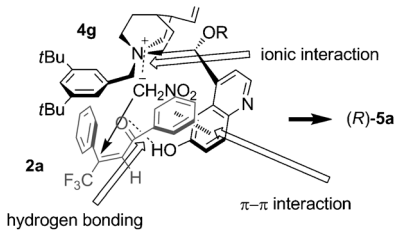
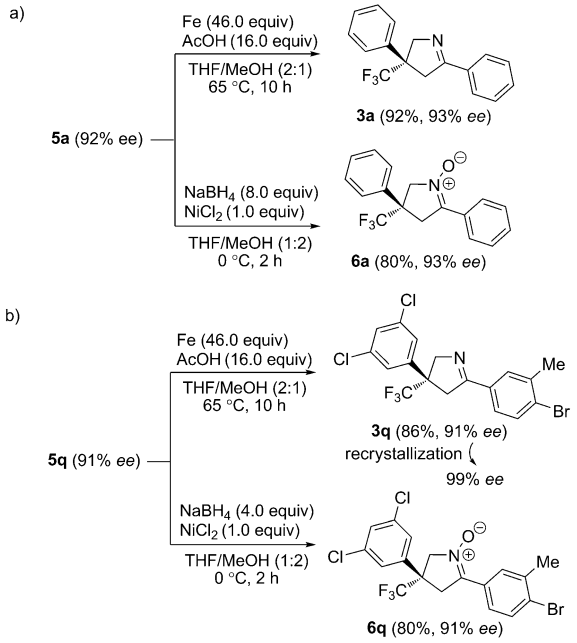


Figure 2. Proposed transition-state model for conversion of **2a** into (*R*)-**5a** catalyzed by **4g**.

Finally, the one-step conversion of **5** into the partially saturated arylpyrrolines **3** and the biologically active polar isostere N-oxide **6** were carried out. The nitro reduction/cyclization/dehydration sequence of **5a** using iron in the presence of acetic acid provided **3a** in high yield (92%) without any loss in the enantiopurity of **5a** (Scheme 2a, top).



Scheme 2. Transformations of **5** to the diarylpyrrolines **3** and N-oxide **6**.

The N-oxide **6a** was synthesized with high chemical yield by treatment of **5a** with $NaBH_4$ in the presence of a stoichiometric amount of $NiCl_2$ in THF/MeOH (1:2) at 0 °C (Scheme 2a, bottom). We next focused on the transformation of the multisubstituted compound **5q** (Scheme 2b). As expected, halogens on the aromatic ring were well tolerated under these reaction conditions, and **3q** and *N*-oxide **6q** were successfully synthesized with high yields of 86 and 80%, respectively. The enantiopurity of the biologically important **3q** easily increased to 99% *ee* by single-crystal recrystallization from *n*-hexane. The diarylpyrroline **3q** could serve as a key intermediate for the synthesis of the potential agrochemicals **7a**[4n] and **7b**[4l] (Figure 3).

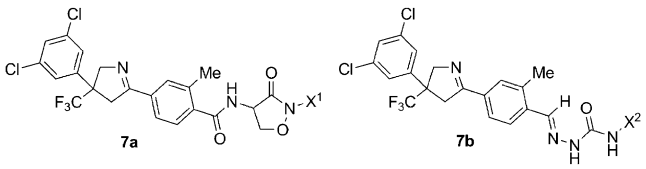


Figure 3. Agrochemicaly important trifluoromethylated pyrrolines **7**.

In summary, we have developed an operationally simple, highly enantioselective conjugate addition of nitromethane to the sterically demanding β-aryl-β-trifluoromethyl-substituted enones **2** catalyzed by the novel cupreidine-based phase-transfer catalyst **4g** to provide conjugate addition adducts having trifluoromethylated all-carbon quaternary stereocenters. Ether-type, 9-OH-protected cupreidinium salts are crucial for this transformation, which gives excellent chemical yields and enantioselectivities (over 90% *ee*). Transformation to the biologically important trifluoromethylated arylpyrrolines **3** and their N-oxide **6** were achieved from the nitromethane adduct **5** with high to excellent yields by a single step. The optically active N-oxides **6** are attractive as polar isosteres of **3** and the biological evaluation of chiral **6** is under investigation.

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