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Improved Asymmetric S_NAr Reaction of β-Dicarbonyl Compounds Catalyzed by Quaternary Ammonium Salts Derived from Cinchona Alkaloids

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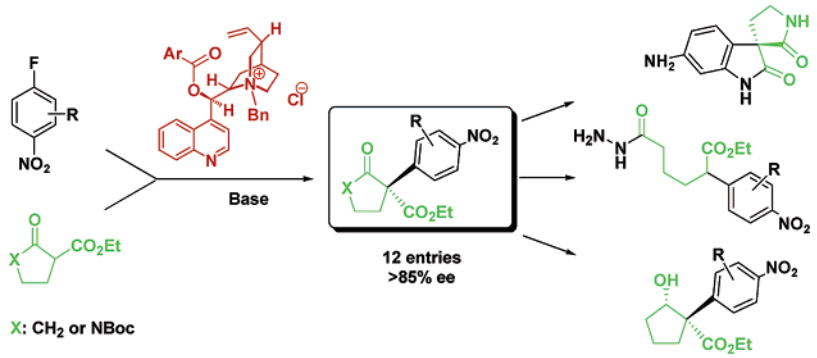

The scope and limitation of the asymmetric nucleophilic aromatic substitution reaction of α-substituted 1,3-dicarbonyl compounds and activated aromatic systems catalyzed by *N*-benzyl-*O*-benzoylcinchoninium or cinchonidinium salts are presented. Several novel *O*-benzoylcinchona alkaloid derived salts have been prepared and evaluated as catalysts in this reaction, which can proceed with enantioselectivites up to 96% ee. Various 1,3-dicarbonyl compounds and activated aromatic systems are evaluated for the aromatic nucleophilic substitution reaction, and it has been found that the yield and enantioselectivity are very dependent on the substrate and reagent. The scope of the functionalization of the products to, e.g., spiro-oxoindole, a ring-opening reaction of 1,3 α,α-disubstituted dicarbonyl compounds with several nucleophiles, and the diastereoselective reduction of the keto functionality in the optically active S_NAr product are reported.

Introduction

A fundamental reaction in organic chemistry is the nucleophilic aromatic substitution reaction (S_NAr) which has been known for more than 100 years.[1] The S_NAr reaction normally requires aromatic compounds having electron-withdrawing substituents in order to activate the "electron-rich" aromatic ring for the nucleophilic attack. A variety of different nucleophiles can be used, including carbon-, oxygen-, and amine-type nucleophiles.[2]

A challenge for the S_NAr reaction is to control the stereochemistry of the formed chiral center when carbon nucleophiles are used, and there are only a limited number of examples in which the stereochemistry of the newly formed chiral center can be controlled.[3] In a recent paper,[4] we reported the first organocatalytic S_NAr reaction of β-ketoesters with activated aromatic compounds to generate chiral quaternary stereocenters[5] using a quaternary ammonium salt derived from cinchona

(1) See, e.g.: (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001; Chapter 13, p 850. (b) Buncel, E.; Dust, J. M.; Terrier, F. *Chem. Rev.* **1995**, *95*, 2261.

(2) See, e.g.: (a) Selvakumar, N.; Yadi Reddy, B.; Sunil Kumar, G.; Iqbal J. *Tetrahedron Lett.* **2001**, *42*, 8398. (b) Snow, R. J.; Butz, T.; Hammach, A.; Kapadia, S.; Morowick, T. M.; Prokopowicz, A. S.; Takahashi, H.; Tan, J. D.; Tschantz, M. A.; Wang, X.-J. *Tetrahedron* **2002**, *43*, 7553. (c) Lawrence, N. J.; Davies, C. A.; Gray, M. *Org. Lett.* **2004**, 26, 4957.

(3) (a) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue T. Y.; Natarajan, S.; Chu, X. J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584. (b) Snyder, S. E.; Shvets, A. B.; Pirkle, W. H. *Helv. Chim. Acta* **2002**, *85*, 3605. (c) Islas-Gonzales, G.; Bois-Choussy, M.; Zhu, J. *Org. Biomol. Chem.* **2003**, *1*, 30.

(4) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670.

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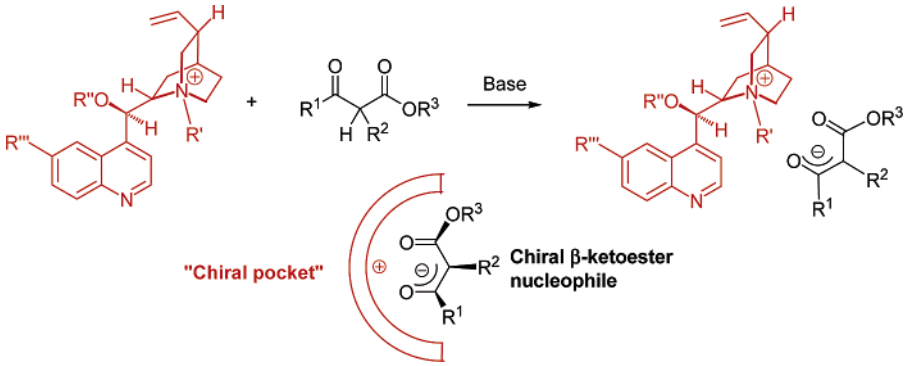


FIGURE 1. Concept of the organocatalytic direct S_NAr reaction of β-keto ester showing the formation of a chiral ion pair by the interaction of a cinchona alkaloid quaternary ammonium salt and the β-keto ester generating a chiral nucleophile in a "chiral pocket".

alkaloids as the catalyst.[6] In the present paper, we present the scope and limitation of this novel asymmetric reaction, together with various transformations of the optically active products such as the synthesis of optically active spiro[pyrrolidone-3,3′-oxoindoles], diastereoselective reductions, and an unusual nucleophilic ring opening reaction of the products.

The organocatalytic direct S_NAr reaction of β-ketoesters is based on the concept outlined in Figure 1 with a cinchona alkaloid quaternary ammonium salt as the chiral catalyst.[7] A base removes the acidic proton in the β-ketoester generating an ambident nucleophile, which interacts with the chiral quaternary ammonium salt forming a chiral ion pair. The idea behind this chiral ion-pair formation is that the chiral cinchona alkaloid salt and the β-ketoester generate a nucleophile in a "chiral pocket" (Figure 1) in which one face is shielded by the chiral cinchona alkaloid salt leading to an enantioselective nucleophilic approach to the aromatic compound.

Results and Discussion

Due to the ambident nature of the nucleophile formed in the reaction, both a carbon and oxygen nucleophile can perform the S_NAr reaction, and the reaction course is very dependent on the R′, R″, and R‴ substituents as outlined in Figure 2.

Our starting point is the reaction of 2-carbethoxycyclopentanone **1a** with 2,4-dinitrofluorobenzene (2,4-DNF) **2a** in a biphasic system consisting of toluene as the solvent and CsOH-monohydrate as the base in the presence of an extensive number of cinchona alkaloid quaternary ammonium salts **4** having a diversity in substitution patterns (eq 1).[8,9] The results from the screening process are presented in Table 1.

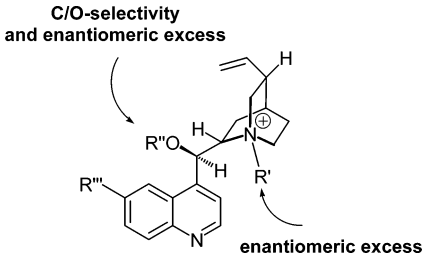


FIGURE 2. Influence of the substituents R′, R″, and R‴ on the reaction course of the organocatalytic enantioselective S_NAr reaction.

It has been found that the regio- and stereoselectivity are very dependent on the substituents R′ and R″. For R′ = Bn or 4-CF_3-Bn and R″ = allyl of the catalysts **4a** and **4b**, respectively, the ambident nature of the nucleophile determines the *C*- vs *O*-arylation selectivity, and mixtures of the *C*- and *O*-arylated products are obtained in ratios of 1.5:1 to 1.0:1 and with very low enantiomeric excess (entries 1 and 2). For the cinchona alkaloid catalyst **4c** having R′ = R″ = Bn, a 1.0:1 ratio between the *C*- and *O*-arylated products is also obtained and the desired product **3a** is formed as a racemate (entry 3). The functionalization of the catalyst turned out to solve both the regio- and enantioselectivity problem of the S_NAr reaction; an exchange of the R″-substituent from benzyl to benzoyl (catalyst **4d**) leads to a dramatic change in both regio- and enantioselectivity; at room temperature, the desired product **3a** is now formed as the major product (*C*-/*O*-arylating ratio 4:1) and with an enantiomeric excess of 46% ee (entry 4). Lowering the reaction temperature to −40 °C leads to a significant improvement to >20:1 in favor of **3a** and now with 87% ee in toluene as the solvent (entry 5). Although we lack a rigorous model to explain the increase in enantiomeric excess, we can hypothesize that a coordinating group near the 9-position (the R″-position) is

(5) For synthesis of asymmetric quaternary stereocenters starting from α-dicarbonyl compounds, see, e.g.: Conjugate addition: (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (b) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. (c) Fanghui, W.; Hongming, L.; Hong, L.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. Conjugate addition to alkynones: (d) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672. Amination: (e) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. Alkylation: (f) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897. (g) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796. Halogenation: (h) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219. (i) Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**, *10*, 2133. Fluorination: (j) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001. Pd-mediated arylation: (k) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (l) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (m) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500.

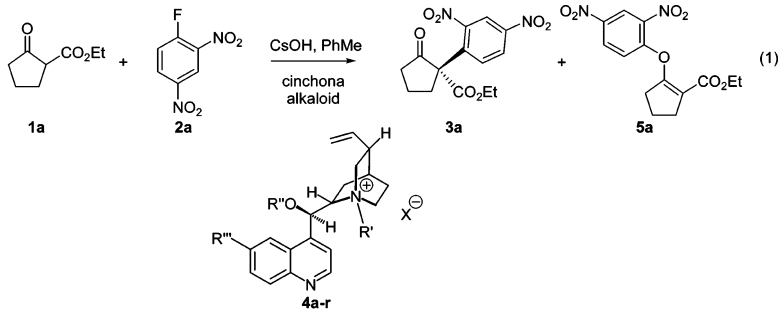
(6) See, e.g.: (a) Halpern, M. E. *Phase-Transfer Catalysis. Mechanism and Synthesis*; American Chemical Society: Washington, DC, 1997. (b) Sasson Y.; Neumann, R. *Handbook of Phase-Transfer Catalysis*; Blackie A&M: London, 1997.

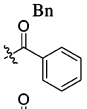
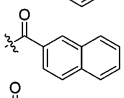
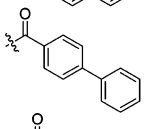
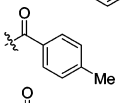
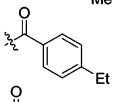
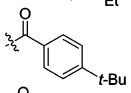
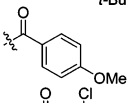
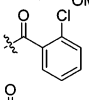
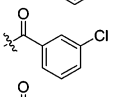
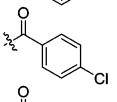
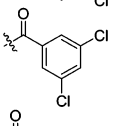
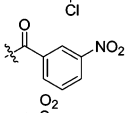
(7) (a) Ooi, T.; Maruoka, K. *Chem. Rev.* **2003**, *103*, 3013. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506.

(8) (a) O'Donnel, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (b) Corey, E. J.; Bo, Y.; Bush-Pedersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000. (c) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 6; 446. For the modifications of cinchona alkaloid-derived PTC catalysts, see: Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961.

(9) For the use of benzoylated quinine derivatives in asymmetric synthesis, see, e.g.: France S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206 and references therein.

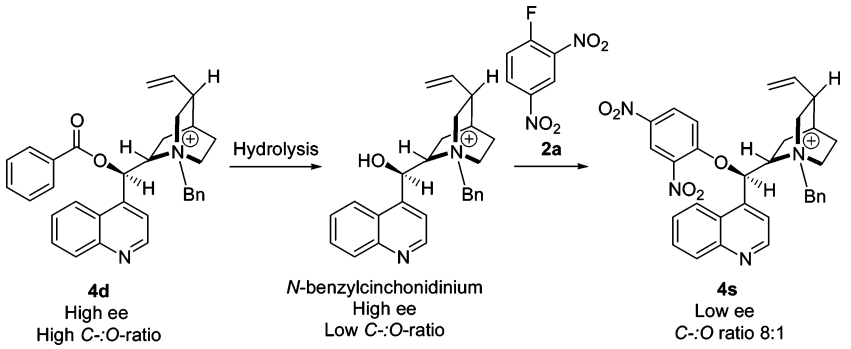
TABLE 1. Screening of Catalysts for the Organocatalytic (15 mol %) S_NAr Addition of 2-Carbethoxycyclopentanone 1a to 2,4-DNF 2a[a]



Entry	Catalyst R'	R''	R'''	X		temp (°C)	*C*-:*O*-arylation[b] ratio	ee[c] (%)
1	Bn	Allyl	H	Br	**4a**	rt	1.5:1	15
2	4-CF_3-Bn	Allyl	H	Br	**4b**[d]	rt	1.0:1	-7
3	Bn	Bn	H	Br	**4c**	-20	1.0:1	rac
4	Bn		H	Cl	**4d**	rt	4:1	46
5	Bn		H	Cl	**4d**	-40	>50:1	87
6	Me[e]		H	I	**4e**	-20	9:1	5[f]
7	Bn[e]		OMe	Cl	**4f**	-20	>20:1	45
8	Bn		H	Cl	**4g**	-20	>20:1	65
9	Bn		H	Cl	**4h**	-20	>20:1	65
10	Bn		H	Cl	**4i**	-20	>20:1	67
11	Bn		H	Cl	**4j**	-20	>20:1	61
12	Bn		H	Cl	**4k**	-20	>20:1	13
13	Bn		H	Cl	**4l**	-20	>20:1	58[f,g]
14	Bn		H	Cl	**4m**	-20	>20:1	64
15	Bn		H	Cl	**4n**	-20	1.4:1	17
16	Bn		H	Cl	**4o**	-40	>20:1	58
17	Bn		H	Cl	**4p**	-20	>20:1	65
18	Bn		H	Cl	**4q**	-20	>20:1	15
19	Bn		H	Cl	**4r**	0	>20:1	5

[a] All reactions were preformed with 0.03 mmol of **4**, 0.20 mmol of **1a**, and 0.25 mmol of **2a** in 4 mL of solvent and 150 mg of CsOH to >90% conversion (<2 h). [b] Ratio determinated by ^1H NMR spectroscopy. [c] Enantiomeric excess determinated by HPLC. [d] *N*-Trifluorobenzyl-*O*-allylcinchonium bromide was used. [e] Low conversion: less than 20% isolated yield. [f] Solvent is PhMe/$CHCl_3$ 9:1. [g] KOH is used as base.

SCHEME 1. Hydrolysis of the Benzoate Ester to the Commercially Available *N*-Benzylcinchonidinium Salt, which Consequently Reacts with 2,4-DNF 2a Present in the Reaction

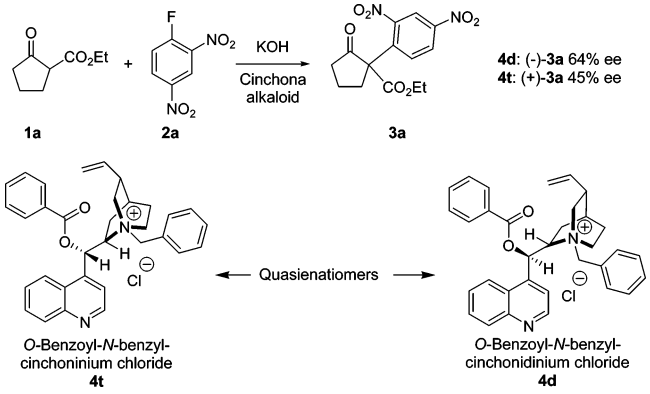


important to achieve high enantioselectivities. Catalyst **4c** (R″ = CH_2Ph), which differs from catalyst **4d** (R″ = C(═O)Ph) for a subtle oxygen atom, gives **3a** as a racemate and 1:1 *C*-/*O*-arylation ratio. It is noteworthy that hydrolysis of the benzoate group is observed with prolonged reaction times (Scheme 1), giving the cinchonidinium salt having a free hydroxyl group, which under the reaction conditions applied quickly reacts with 2,4-DNF **2a** to form the new catalyst **4s**. We have observed that the *N*-benzylcinchonidinium salt with the free hydroxyl group can also catalyze the S_NAr reaction presented in eq 1 and using 50 mol % of the catalyst up to 70% ee of **3a** was obtained. Unfortunately, this result is not reproducible; the high enantioselectivity varies apparently with the rate of the addition of catalyst. More disappointing, the *C*- vs *O*-arylation ratio is 1:9; therefore, even if a reliable protocol for performing this reaction could have been developed, it would have little synthetic value considering the low yield of **3a**. The phase transfer catalyst having the 2,4-dinitro phenyl group in the 9-position (catalyst **4s**) is also catalyzing the S_NAr reaction; however, with low enantioselectivity, 44% ee, but with some regioselectivity, in favor of the desired product *C*-/*O*-arylation ratio 8:1 at −40 °C. The success of this S_NAr reaction is thus related to avoiding the hydrolysis of the ester group in the catalyst.

With the successful S_NAr reaction using **4d** as the catalyst, we decided to test a number of related catalysts by varying the R′ and ester group R″ (Table 1, entries 6−19). With catalyst **4f**, lower enantiomeric excess is obtained compared to the catalyst having the hydrogen atom in the R‴-position (entry 7).

The enantioselectivity of the S_NAr reaction is eroded when the R′ benzyl group is exchanged with a methyl group (catalyst **4e**); however, the regioselectivity is maintained to some extent with the *C*-arylated product **3a** as the major compound 9:1 *C*-/*O*-arylation ratio (entry 6). Further investigations revealed that the naphthyl or biphenyl catalysts, **4g** and **4h**, respectively, gave a slight increase in enantiomeric excess of **3a** to 65% ee, while maintaining the high *C*- to *O*-arylation selectivity (entries 8 and 9). Under the present reaction conditions, substitution in the para position with alkyl groups has a large influence on the enantioselectivity of the reaction: Me (**4i**), 67% ee; Et (**4j**), 61% ee; *t*-Bu (**4k**), 13% ee; and OMe (**4l**), 58% ee (entries 10−13). The enantioselectivity is also very dependent on the substitution position in the phenyl ring, moving the chloro substituent from the ortho- (**4m**) to the meta- (**4n**) and to the para-position (**4o**) gives the following results: 64% ee, 17% ee, and 58% ee, respectively (entries 14−16). It is remarkable though that having two chloro substituents in the two meta-positions (**4p**) leads to a reaction with 65% ee (entry 17). An exchange of the chloro substituent in the meta-position (**4n**) with a nitro substituent—catalyst **4p**—leads to a significant lowering in the enantiomeric excess of **3a** to only 15% ee (entry 18). Placing other functionalities in the 9-*O*-position of the catalyst, such as a sulfone (**4r**), provided catalysts which are much less effective, compared to those with ester functionalities (entry 19) under the reaction conditions tested.

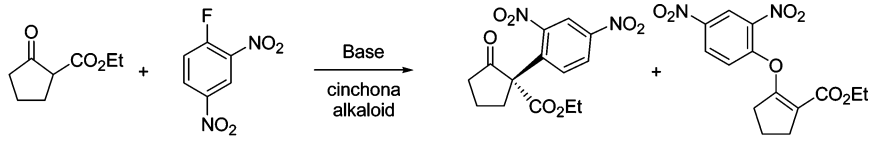
SCHEME 2. S_NAr Addition of 2-Carbethoxycyclopentanone 1a to 2,4-DNF 2a Preformed by the Quasienantiomers 4d and 4t



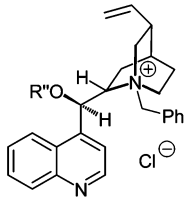
Virtually all of the catalysts (**4a**,**c**−**r**) we have presented so far are based on the cinchonidinium salt. The opposite enantiomer of the product is obtained when the quasienantiomer **4t** is applied as the catalyst (Scheme 2). This catalyst (**4t**) affords up to 45% ee of **3a** in the S_NAr reaction of 2-carbethoxycyclopentanone **1a** and 2,4-DNF **2a**, which is a lower enantioselectivity compared to the cinchonidinium salt **4d** (64% ee).

The solvent is of importance for the organocatalytic direct S_NAr reaction, and we have previously used a 1:9 mixture of $CHCl_3$ and toluene as the reaction solvent, achieving up to 64% ee of **3a** at −20 °C. With prolonged reaction times, precipitation of catalyst **4d** is observed, and moreover some hydrolysis of the benzoate group in the 9-position was detected. After extensive solvents and base screening, we have found that a mixture of CH_2Cl_2/PhMe 1:4, solid KOH as the base, and performing the reaction at −40 °C were the optimal reaction conditions (Table 2). In this case, little or no hydrolysis of the catalyst can be detected. Furthermore, with this new reaction protocol, virtually all of the catalyst is soluble, which might account for the increased enantioselectivity and Table 2 shows the results for the asymmetric S_NAr reaction using various catalysts **4d**,**i**,**k**−**m**,**r**. The effect of changing the inorganic base

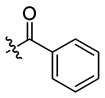
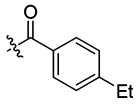
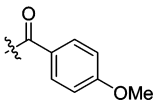
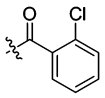
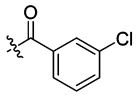
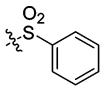
TABLE 2. Screening of Conditions and Catalysts (15 mol %) in the S_NAr Reaction of 2-Carbethoxycyclopentanone 1a to 2,4-DNF 2a[a]



1a **2a** **3a** **5a**



4d,i,k-m,r

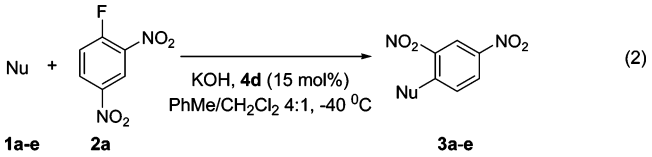
Entry	R''		temp (°C)	solvent	base	ee[b] (%)
1		**4d**	-40	PhMe	CsOH	87
2	-	**4d**	-40	PhMe/CH_2Cl_2 4:1	KOH	85
3		**4i**	-20	PhMe	CsOH	61
4	-	**4i**	-40	PhMe/CH_2Cl_2 4:1	KOH	93
5		**4k**	-20	PhMe/$CHCl_3$ 9:1	KOH	58
6	-	**4k**	-40	PhMe/CH_2Cl_2 4:1	KOH	93
7		**4l**	-20	PhMe	CsOH	64
8	-	**4l**	-40	PhMe/CH_2Cl_2 4:1	KOH	95
9		**4m**	-20	PhMe	CsOH	17
10	-	**4m**	-40	PhMe/CH_2Cl_2 4:1	KOH	96
11		**4r**	0	PhMe	CsOH	5
12	-	**4r**	-40	PhMe/CH_2Cl_2 4:1	KOH	92

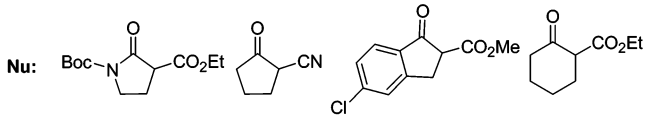
[a] All reactions were performed with 0.03 mmol of **4**, 0.20 mmol of **1a**, and 0.25 mmol of **2a** in 4 mL of solvent and 150 mg of solid base to >90% conversion (<2 h). [b] Enantiomeric excess determined by HPLC.

is very modest, and KOH was preferred because (i) it increased the enantiomeric excess slightly and (ii) it is less hygroscopic.

The results for the 9-*O*-benzoate catalysts **4d**,**i**,**k**−**m**,**r** tested in the S_NAr reaction of 2-carbethoxycyclopentanone **1a** and 2,4-DNF **2a** in Table 2 show some interesting changes; while several *N*-benzyl benzoate catalysts afforded a range of different enantioselectivities of **3a**, varying from 5 to 87% ee, with the previously reported conditions, every catalyst tested with the

TABLE 3. Regio- and Enantioselective S_NAr Reaction of Various Nucleophiles 1a−e to 2,4-DNF 2a Catalyzed by 4d (15 mol %)[a]





Entry	nucleophile	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	2	**3a**, 78	85
2	**1b**	24	**3b**, 93[d]	85
3	**1c**	5	**3c**, 16	60
4	**1d**	21	**3d**, 36	35
5	**1e**	5	**3e**, 20[e]	38

[a] Experimenal conditions: 0.06 mmol of **4d**, 0.40 mmol of **1**, and 0.50 mmol of **2a** in 8 mL of solvent (CH_2Cl_2/PhMe 1:9) and 300 mg of KOH at −40 °C. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC. [d] Reaction mixture PhMe/$CHCl_3$ 9:1. [e] 16% *O*-arylated product is also obtained (**5e**).

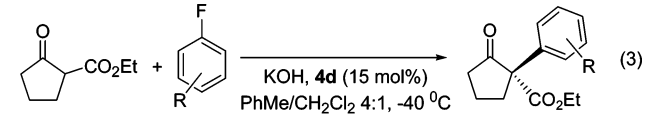
new protocol performed significantly better, within 85−96% ee (Table 2, entries 1−10), and in one case—catalyst **4r**—the enantiomeric excess increased from 5 to 92% ee (entries 11 and 12). Previously, the chloride-substituted catalyst gave very different enantioselectivities depending on the position of the chloride: the ortho-substituted catalyst **4l** gave 64% ee, whereas the meta-substituted catalyst **4m** provided **3a** in only 17% ee, while under the new conditions they afforded 95 and 96% ee, respectively (entries 7−10).

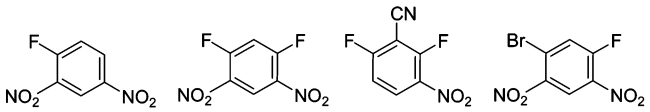
Expanding the system to other nucleophiles and electrophiles has been attempted. Various nucleophiles have been tested (Table 3), and it turns out that the reaction proceeds best for nucleophiles containing a five-membered ring such as **1a−c** where enantioselectivities in the range of 60−85% ee are obtained (Table 3, entries 1−3). However, it should be noted that an exchange of the ester group in **1a** with a cyano group (**1c**) leads to a significant drop in the yield of the reaction to only 16%; however, the enantiomeric excess of product **3d** was still satisfactory (60% ee, entry 3). Furthermore, it seems there is a limit to the size of the nucleophiles in the case of **1d**, a bulky nucleophile, that reduces the enantiomeric excess to only 35% ee (entry 4). Expanding to a six-membered ring (**1e**), the enantiomeric excess declines to 38% ee and the reaction is less selective regarding the *C*-/*O*-arylation, as a ratio of 1.3:1 is found.

Variation within the electrophiles is also possible as presented in Table 4, and the reaction proceeds with high stereoselectivity. It is important to have a strong electron-withdrawing group in the para-position relative to the substitution site and in all case this is achieved via a nitro group. In the case where there are two dissimilar fluorides (**2c**), the reaction is regioselective and the reaction proceeds with substituting only the fluoride, para to the nitro group (Table 4, entry 3). It appears also from the results in Table 4 that different groups can be attached to the aromatic ring (**2a−d**), still maintaining high regioselectivity and enantioselectivities in the range 85−94% ee.

The products formed via S_NAr reaction have a variety of applications, and we examined possible functionalization of

TABLE 4. Organocatalyzed Asymmetric *C*-Selective S_NAr Reaction of *β*-Ketoester 1a with Different Electrophiles 2a−d Catalyzed by 4d (15 mol %)[a]

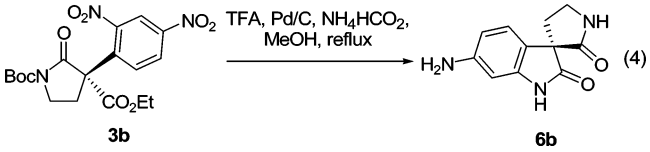




entry	electrophile	yield[b] (%)	ee[c] (%)
1	**2a**	**3a**, 78	85
2	**2b**	**3f**, 76	90
3	**2c**	**3g**, 68	90
4	**2d**	**3h**, 76	94

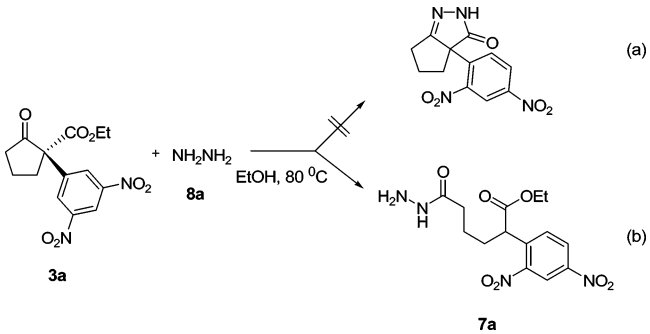
[a] Experimental conditions: 0.05 mmol of **4d**, 0.30 mmol of **1a**, and 0.38 mmol of **2** in 6 mL of solvent (CH_2Cl_2/PhMe 1:9) and 225 mg of KOH at −40 °C. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC.

these products. We have previously shown[4] that the products are, e.g., precursors of oxoindoles bearing a chiral quaternary carbon center a motif present in numerous natural substances.[10] The enantioselective approach toward this class of molecules was presented by the one-pot synthesis (four step reaction: *N*-Boc-removal, reduction of two nitro groups and ring closure) of the spiro[pyrrolidone-3,3′-oxoindole] **6b** in 70% yield from compound **3b** (eq 4).



Another class of interesting compounds is pyrazoles, and the *β*-ketoesters might be ideal candidates for creating chiral pyrazoles (Scheme 3a).[11]

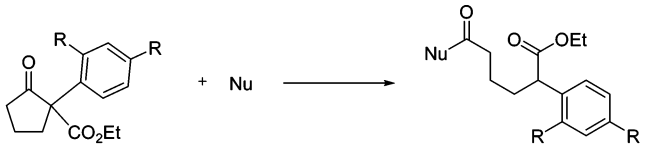
SCHEME 3 [a]



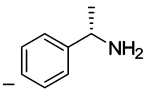
[a] The expected reaction of *β*-ketoesters of the S_NAr reaction with hydrazine in a ring-closing fashion creating a pyrazole. [b]The unpredicted formation of 2-(2,4-dinitrophenyl)-5-hydrazinocarbonylpentanoic acid ethyl ester **7a**.

We expected that the chiral α,α-disubstituted *β*-ketoesters should be able to condensate with hydrazine, thereby giving access to chiral pyrazoles via hydrazone formation and a ring-closure reaction. When the chiral α,α-disubstituted-*β*-ketoester

TABLE 5. Opening of α,α-Disubstituted Aryl β-Ketoesters with a Selection of Nucleophiles



3a,i **8a-c** **7a-d**

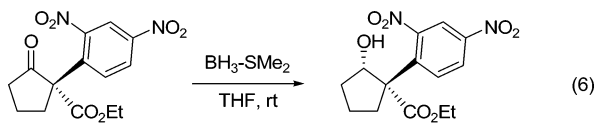
Entry	R	temp (°C)	solvent	time (h)	Nu	yield (%)[a]
1	**3a** – NO_2	80	EtOH	2	**8a** – NH_2NH_2	**7a** – 84
2	**3a** – NO_2	80	EtOH	3	**8b** – NaOEt	**7b** – 49
3	**3i** – H	rt	EtOH	24	**8a** – NH_2NH_2	**7c** – 35[b]
4	**3a** – NO_2	rt	THF	192	**8c** – 	**7d** – 65[b]

[a] Isolated yield. [b] Estimated by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield not determined due to the small scale of the reaction.

3a was treated with hydrazine hydrate complete conversion occurred and formation of a highly polar product was observed using TLC; however, this product was not the expected pyrazole, but a compound (**7a**) resulting from an unpredicted nucleophilic ring opening of the cyclopentanone ring in **3a** (Scheme 3b).[12]

This unexpected reaction prompted us to test several nucleophiles for this ring opening, and the results are presented in Table 5. All nucleophiles afforded the open-chain compound **7**. The reaction of **3a** with hydrazine hydrate (Table 5, entry 1) or NaOEt (entry 2) afforded the ring-opened product **7a**,**b** in moderate to good yields within a few hours. Electron-withdrawing groups on the aromatic ring are not essential (entry 3), since **3i** also afford the opened product 2-phenyl-5-hydrazinocarbonylpentanoic acid ethyl ester (**7c**). The α,α-disubstituted β-ketoester **3a** was additionally reacted with a chiral amine (**8c**) to investigate if the reaction revealed any diastereoselectivity (entry 4); this was sadly not the case. Compounds of class **7** are chiral, but regardless of the grade of enatiopurity of the starting material they are obtained as racemates. While in the past few years numerous protocols for the synthesis of chiral nonracemic α,α-disubstituted β-ketoesters appeared in the literature,[5] these competing ring-opening reactions constitute a limit to the possible functionalization of the products, without losing the enantiomeric excess of the chiral compound just formed.

Another interesting functionalization of the products formed through S_NAr reaction would be the β-hydroxy compounds. Herein, we present a diastereoselective reduction of optically active α,α-disubstituted aryl-β-ketoester **3a** to α-hydroxylester **9a** (eq 6). This anti-diastereoselective reduction of **3a** was achieved with borane dimethyl sulfide complex (BH_3−DMS) in THF to afford a single diastereoisomer **9a**, albeit in low yields.



3a (44% ee) **9a** (31% ee, 32% yield)

In conclusion, we have reported in full our investigation on the asymmetric S_NAr reaction catalyzed by benzoylated cinchona alkaloid salts. Good enantiomeric excess can be obtained if a catalyst capable of two-site binding is employed; however, so far a catalyst able to achieve vast generality of the nucleophile has not been found. A large number of chiral cinchona alkaloid salts can catalyze the model reaction with high selectivity, both in terms of *C*- vs *O*-selectivity and enantiomeric excess; however, the asymmetric S_NAr reaction of different nucleophiles is dependent on the structure of the nucleophile, and it turns out that the reaction proceeds best for nucleophiles containing a five-membered ring. Variation of the electrophile is viable, and high regioselectivity and enantioselectivities of 85−94% ee are obtained. The products formed via S_NAr reaction, reacts with different nucleophiles in an unexpected nucleophilic ring opening reaction, and another possible functionalization of these products is the diastereoselective reduction of an optically active α,α-disubstituted aryl-β-ketoester to the β-hydroxyester.

Experimental Section

General Procedure for the Enantioselective S_NAr Reaction of Aromatic Fluorides 2a−d with Nucleophile 1a−e Catalyzed by 4a−t. In a test tube, the catalyst **4** (0.03 mmol, 15 mol %) was dissolved in CH_2Cl_2 (0.8 mL), and nucleophile **1a**−**e** (0.20 mmol, 1.00 equiv), aromatic fluoride **2a**−**d** (0.25 mmol, 1.25 equiv), and PhMe (3.2 mL) were added. Another test tube contained KOH (150 mg). The test tubes were cooled to the indicated temperature, and KOH was added to the reaction mixture. The test tube was closed by a rubber septa; no inert atmosphere was used. The reaction mixture was stirred at the indicated temperature until no starting nucleophile could be detected by TLC. The crude mixture was directly purified by FC to afford pure products **3a**−**h**. The enantiomeric excess was determined by HPLC.

3a: yield 89%; ^{1}H NMR δ ($CDCl_3$) 8.78 (d, 1H, *J* 2.4 Hz), 8.34 (dd, 1H, *J* 8.8 Hz, *J* 2.0 Hz), 7.41 (d, 1H, *J* 8.8 Hz), 4.12 (q, 1H,

(10) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *42*, 2209 and references therein.

(11) See, e.g.: (a) Sircar, I.; Morrison, G. C.; Burke, S. E.; Skeean, R.; Weishaar, R. E. *J. Med. Chem.* **1987**, *30*, 1724. (b) Jenwitheesuk, E.; Samudrala, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3989. (c) Kees, K. L.; Fitzgerald, J. J., Jr.; Steiner, K. E.; Mattes, J. F.; Mihan, B.; Tosi, T.; Mondoro, D.; McCaleb, M. L. *J. Med. Chem.* **1996**, *39*, 3920 and references therein.

(12) For a related reaction, see: Cort, L. A.; Mahesar, M. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2034.

J 7.2 Hz), 4.11 (q, 1H, *J* 7.2 Hz), 3.2−3.1 (m, 1H), 2.8−2.6 (m, 1H), 2.6−2.2 (m, 3H), 2.1−1.9 (m, 1H), 1.14 (t, 3H, *J* 7.2 Hz); ^{13}C NMR δ ($CDCl_3$) 211.3, 168.1, 149.4, 147.2, 140.5, 131.5, 127.4, 121.5, 65.4, 63.0, 38.9, 37.0, 19.6, 14.1; HRMS calcd for $C_{14}H_{14}N_2NaO_7$ 345.0699, found 345.0699; $[\alpha]^{rt}_D = -40$ (*c* 4.05, $CDCl_3$, 56% ee) (optical rotation performed from another reaction than reported in Table 1). The ee was determined by HPLC using Chiralpak AS column (hexane/*i*-PrOH 80:20); flow rate 1.0 mL/min; $\tau_{major} = 12.5$ min; $\tau_{minor} = 15.4$ min.

General Procedure for Opening of α,α-Disubstituted Aryl *β*-Ketoesters with Various Nucleophiles to 7a,b,d. The *β*-ketoester (50 mg (**3a**), 0.155 mmol, 1.0 equiv), nucleophile (0.165 mmol, 1.1 equiv), and solvent (2 mL) were combined in a test tube with a magnetic stir bar and maintained at the indicated temperature until no *β*-ketoester could be detected by TLC. The crude mixture was directly purified by FC to afford pure products **7a**,**b**,**d**.

7a: yield 84%; ^{1}H NMR δ ($CDCl_3$) 8.72 (d, 1H, *J* 2.1 Hz), 8.41 (dd, 1H, *J* 8.6 Hz, *J* 2.0 Hz), 7.78 (d, 1H, *J* 8.6 Hz), 7.21 (bs, 1H), 4.23 (t, 1H, *J* 7.3 Hz), 4.2−4.1 (m, 2H), 3.64 (bs, 2H), 2.3−2.1 (m, 3H), 2.0−1.9 (m, 1H), 1.8−1.5 (m, 2H), 1.71 (t, 3H, *J* 7.1 Hz); ^{13}C NMR ($CDCl_3$) 172.8, 171.1, 149.3, 146.7, 139.9, 131.5, 127.1, 120.2, 61.8, 46.3, 33.4, 32.0, 23.1, 13.9; HRMS calcd $C_{14}H_{18}N_4NaO_7$ 377.1073, found 377.1068.

Aryl *β*-Ketoester (3a) to *β*-Hydroxy Ester (9a). To a solution of *β*-ketoester (**3a**) (113 mg, 0.35 mmol, 1.00 equiv) in THF (5 mL) was added 3 equiv of BH_3−DMS complex (0.105 mL, 1.05 mmol, 3.00 equiv). After being stirred at room temperature for 7 d, to the reaction mixture was added dropwise 1 mL of 1 M HCl and the solution extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude reaction mixture was purified by FC (Et_2O/pentane 2:1) to give the optically active *β*-hydroxy ester **9a**. The enantiomeric excess was determined by HPLC.

9a: yield 32%; ^{1}H NMR δ ($CDCl_3$) 8.70 (d, 1H, *J* 2.1 Hz), 8.44 (dd, 1H, *J* 8.8 Hz, *J* 1.5 Hz), 8.01 (d, 1H, *J* 8.8 Hz), 4.55 (t, 1H, *J* 6.9 Hz), 4.20 (dq, 2H, *J* 7.1 Hz, *J* 2.9 Hz), 3.12 (bs, 1H), 2.79 (ddd, 1H, *J* 13.6 Hz, *J* 9.9 Hz, *J* 6.5 Hz), 2.1−2.0 (m, 1H), 2.0−1.8 (m, 3H), 1.7−1.6 (m, 1H), 1.19 (t, 3H, *J* 7.1 Hz); ^{13}C NMR ($CDCl_3$) 172.6, 149.1, 146.6, 143.9, 131.0, 126.9, 120.6, 79.7, 62.0, 59.7, 33.5, 32.3, 19.7, 13.9; HRMS calcd $C_{14}H_{16}N_2NaO_7$ 347.0855, found 347.0858; $[\alpha]^{rt}_D = +57$ (*c* 2.47, CH_2Cl_2, 31% ee). The ee was determined by HPLC using a Chiralpak AS column (hexane/*i*-PrOH 80:20); flow rate 1.0 mL/min; $\tau_{major} = 6.9$ min; $\tau_{minor} = 8.0$ min.

Acknowledgment. This work was made possible by a grant from the Danish National Research Foundation. Thanks are expressed to a reviewer for drawing our attention to ref 12.

Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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