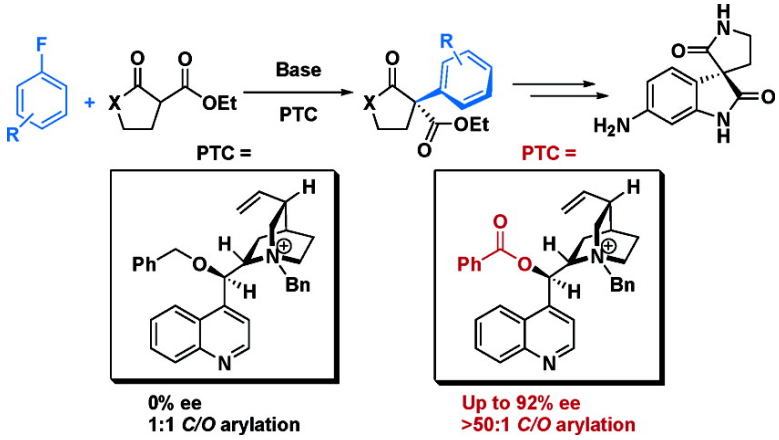
Communication

# Organocatalytic Regio- and Asymmetric *C*-Selective SAr ReactionsStereoselective Synthesis of Optically Active Spiro-pyrrolidone-3,3‘-oxoindoles

Marco Bella, Sara Kobbelgaard, and Karl Anker Jrgensen

*J. Am. Chem. Soc.*, **2005**, 127 (11), 3670-3671• DOI: 10.1021/ja050200g • Publication Date (Web): 23 February 2005






## More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 13 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 02/23/2005

# Organocatalytic Regio- and Asymmetric *C*-Selective $S_NAr$ Reactions—Stereoselective Synthesis of Optically Active Spiro-pyrrolidone-3,3′-oxoindoles

Marco Bella, Sara Kobbelgaard, and Karl Anker Jørgensen*

*Danish National Research Foundation, Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark*

Received January 12, 2005; E-mail: kaj@chem.au.dk

The nucleophilic aromatic substitution ($S_NAr$) reaction is a fundamental transformation in organic chemistry.[1] The nucleophiles employed are mostly amines or phenols, but 1,3-dicarbonyl compounds are reactive enough to be arylated under mild conditions.[2]

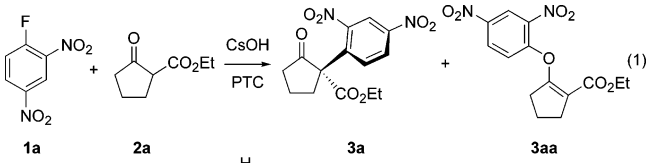
Although the nucleophilic aromatic substitution reaction has been known for more than 100 years, there are only sporadic examples, restricted to intramolecular reactions and oxygen nucleophiles, in which the stereochemistry of the newly formed center is controlled.[3] To the best of our knowledge, there are no reports of chiral induction on quaternary or tertiary stereocenters formed when carbon nucleophiles are applied. Furthermore, no catalytic highly enantioselective $S_NAr$ reactions have been developed to our knowledge.

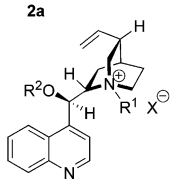
Herein, we present the development of the organocatalytic regio- and enantioselective $S_NAr$ reaction between activated aromatic compounds and 1,3-dicarbonyl compounds using phase transfer catalysis (PTC).[4,5] This new reaction affords functionalized optically active compounds bearing a quaternary stereocenter[6] in high enantioselectivities, in excellent yields, and with high atom economy, using simple operations and mild and environmentally benign reaction conditions. Furthermore, we demonstrate the utility of this new reaction by the synthesis of the optically active spiro-pyrrolidone-3,3′-oxoindole structure, which constitutes the skeleton of a wide range of natural substances and pharmaceutically interesting molecules.[7]

The use of PTC-mediated reactions using cinchona alkaloids has focused on mainly the alkylations of glycine derivatives toward the synthesis of natural or unnatural amino acid derivatives,[8] and only recently have synthetically useful procedures for the asymmetric PTC-mediated alkylation of 1,3-dicarbonyl compounds been reported.[9,10]

Our starting point for the enantioselective $S_NAr$ reaction is the addition of commercially available 2,4-dinitro-fluorobenzene (2,4-DNF, **1a**) to 2-carboethoxy-cyclopentanone **2a** in a biphasic system consisting of an organic solvent and CsOH monohydrate as the base (Table 1). Complete conversion after a few minutes at room temperature was obtained upon the addition of a quaternary ammonium salt catalyst, such as TBAI or the cinchona alkaloid derivative ammonium salt **4a**.[11a] However, the enantiomeric excess of **3a** was disappointing (entry 2). An initial screening of the most widely used modified cinchona catalysts, e.g., those bearing a hindering 9-anthracenylmethyl group at the quinuclidine nitrogen atom (**4b**, Corey's catalyst)[11b] or a strongly electron-withdrawing group (**4c**),[11c] afforded also only nearly racemic products (entries 3−6). It is well known that catalysts **4b**,**c** improve the enantioselectivity in alkylation reactions compared with **4a** or **4d**.[11c] Moreover, the yield of the desired *C*-arylated product **3a** was affected by formation of the *O*-arylated adduct **3aa** (*C*-arylation vs *O*-arylation 1.5:1). The presence of the *O*-arylated product **3aa** was unexpected, since in the PTC reaction of **2a** with alkyl bromides no formation of the corresponding *O*-alkylated products has been reported. These results suggested that to be able to control the regio- and enantioselectivity of the $S_NAr$ reaction represents a novel and challenging problem, for which the knowledge previously gathered in the alkylation reactions was insufficient.

***Table 1.*** Screening of Catalysts and Conditions for the Organocatalytic (15 mol %) $S_NAr$ Addition of 2-Carboethoxy-cyclopentanone **2a** to 2,4-DNF **1a**[a]




**4a**: $R^1$ = Bn, $R^2$ = allyl, X = Br
**4b**: $R^1$ = 9-anthracenylmethyl, $R^2$ = allyl, X = Br
**4c**: $R^1$ = 4-$CF_3$-Bn, $R^2$ = allyl, X = Br
**4d**: $R^1$ = Bn, $R^2$ = Bn, X = Br
**4e**: $R^1$ = Bn, $R^2$ = Bz, X = Cl

| entry | catalyst (temp, °C) | *C*-:*O*-arylation ratio[b] | yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|
| 1 | TBAI (rt) | 1.5:1 | 90 | |
| 2 | **4a** (rt) | 1.5:1 | 80 | 15 |
| 3 | **4b** (rt) | 1.5:1 | 80 | 10 |
| 4 | **4c** (rt)[e] | 1.0:1 | 70 | −7 |
| 5 | **4d** (rt) | 1.0:1 | 90 | rac |
| 6 | **4d** (−20) | 1.0:1 | 90 | rac |
| 7 | **4e** (rt) | 4.0:1 | 82 | 46 |
| 8 | **4e** (0) | 8.0:1 | 85 | 60 |
| 9 | **4e** (−20) | 16:1 | 89 | 80 |
| 10 | **4e** (−40) | >50:1 | 89 | 87 |

[a] Reaction performed with 0.10 mmol of **2a** and 0.11 mmol of **1a** in 2 mL of toluene; 99% conversion in all reactions after 2 h. [b] Determined by $^1$H NMR. [c] Combined yield of **3a** and **3aa**. [d] Enantiomeric excess determined by HPLC. [e] *N*-Trifluorobenzyl *O*-allyl cinchoninium bromide was used.

High enantioselectivities observed in the PTC-mediated reactions normally arise from electrostatic interactions in the ion pair between the quaternary ammonium salt and the nucleophile, which then reacts in a stereocontrolled manner with the electrophile.

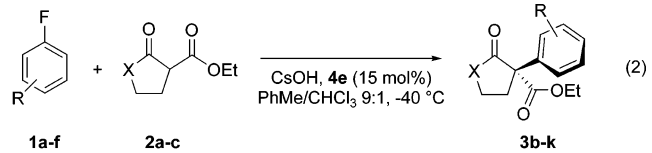
Further screening revealed that the *O*-benzoylated catalyst **4e**,[12] in which the oxygen atom of the benzoyl group might stabilize an ion pair by hydrogen bonding, significantly increased the *C*-arylation selectivity. We were pleased to find that performing the reaction of **1a** with **2a** in the presence of **4e** as the catalyst gave the desired *C*-arylated product **3a** in high yield with a *C*-arylation:*O*-arylation ratio of >50:1 and an enantiomeric excess of up to 87% ee (Table 1, entries 7−10). In Table 1, entries 2, 5, and 6, the known and commercially available *O*-allylated or *O*-benzylated catalysts **4a** and **4d**, respectively, are compared to the *O*-benzoylated catalyst **4e**, showing that the latter represents the solution to increase the enantioselectivity and the *C*-:*O*-arylation ratio in the $S_NAr$ reaction.[13]

In Table 2, the generality of the catalytic enantioselective $S_NAr$ reaction is demonstrated for various aromatic substrates reacting with different nucleophiles.

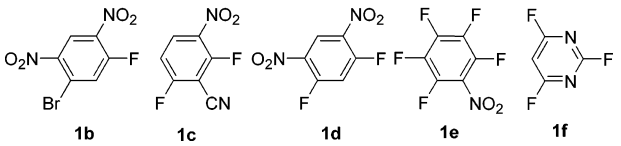


10.1021/ja050200g CCC: $30.25 

***Table 2.*** Enantioselective $S_NAr$ Reaction of Aromatic Fluorides **1a**−**f** with $\beta$-Dicarbonyl Compounds **2a**−**c** Catalyzed by **4e** (15 mol %)




**1a-f** **2a-c** **3b-k**



**1b** **1c** **1d** **1e** **1f**

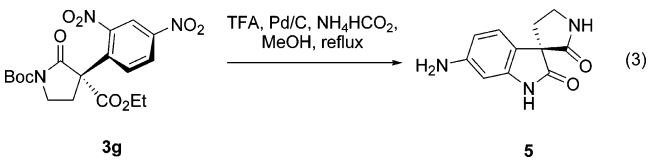
| entry | aromatic fluoride | X | time (h) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **1b** | −$CH_2$−, **2a** | 24 | **3b**, 96 | 92 |
| 2 | **1c** | −$CH_2$−, **2a** | 48 | **3c**, 81[c,d] | 86 |
| 3 | **1d** | −$CH_2$−, **2a** | 24 | **3d**, 81 | 87 |
| 4 | **1e** | −$CH_2$−, **2a** | 24 | **3e**, 65[d] | 70 |
| 5 | **1a** | −NMe−, **2b** | 24 | **3f**, 78[e] | 25 |
| 6 | **1a** | −NBoc−, **2c** | 24 | **3g**, 93 | 85 |
| 7 | **1b** | −NBoc−, **2c** | 48 | **3h**, 84 | 69 |
| 8 | **1c** | −NBoc−, **2c** | 72 | **3i**, 76 | 75 |
| 9 | **1f** | −NBoc−, **2c** | 48 | **3j**, 65[d] | 68 |

[a] Isolated yield. [b] Enantiomeric excess determined by HPLC. [c] Reaction temperature = 35 °C. [d] Isomer in the 4-position (see Supporting Information). [e] Reaction temperature = 20 °C.

The different aromatic compounds **1b**−**e** react with 2-carboethoxy-cyclopentanone **2a** to give the desired products in good to high yields and with up to 92% ee (entries 1−4). Lactams, such as pyrrolidone **2b**, undergo smoothly the $S_NAr$ reaction; however, an enantioselectivity of only 25% ee was found (entry 5). To achieve high enantiomeric excesses, it was necessary to protect the nitrogen atom with the Boc group (**2c**), and then the reaction gave the optically active aromatic substitution product **3g** in very high yield (93%) and 85% ee (entry 6). The other aromatic compounds **1b**,**c**,**f** also reacted smoothly with **2c** (entries 7−9). Less activated aromatic eletrophiles (4-nitro-fluorobenzene) or aromatic compounds bearing a leaving group different than fluorine (2,4-dinitro-chorobenzene) gave only traces of the desired adducts.

All the adducts **3a**−**i**, bearing one or more nitro groups, are solids and the enantiomeric excess can be increased up to 99% ee upon recrystallization. The crystals obtained from **3h** were suitable to determine the absolute configuration by X-ray analysis.[14] The absolute configuration is shown in eq 2.

The products formed have a broad range of applications, e.g. precursor of oxoindoles bearing a chiral quaternary carbon center. This motif is present in numerous natural substances,[7] and this work paves the way to an easy new enantioselective approach toward this class of molecules. Herein, we present a relevant example, 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] **5** from compound **3g** (entry 6). The formation of **5** is achieved in 70% yield (eq 3).




**3g** **5**

In conclusion, herein is reported an unprecedented example of an efficient asymmetric organocatalytic nucleophilic aromatic substitution reaction. A dramatic improvement of regioselectivity and enantioselectivity has been achieved by exchanging a benzyl with a benzoate group in the cinchona alkaloids-derived PTC. The reactions proceed in high yields, with excellent regioselectivity and high enantioselectivities, with several commercially available activated aromatic compounds. This new reaction provides an easy access to optically active dihydroindoles bearing a chiral quaternary carbon. Further studies are in progress to elucidate the mechanism and the origin of enantioselectivity.

**Acknowledgment.** This work was made possible by a grant from The Danish National Research Foundation. Thanks are expressed to Dr. Jacob Overgaard for X-ray analysis.

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

## References

(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. Acta* **2002**, *85*, 3605. (c) Islas-Gonzales, G.; Bois-Choussy, M.; Zhu, J. *Org. Biomed. Chem.* **2003**, *1*, 30.

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

(5) For the Pd-mediated enantioselective arylation of enolates, see: (a) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (b) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500.

(6) See e.g.: (a) Christoffers, M.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(7) For the synthesis of oxoindoles, see, e.g.: Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *42*, 2209 and references therein.

(8) (a) Maruoka K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961.

(9) (a) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897. (b) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796.

(10) Some representative examples for the formation of quaternary stereocenters starting from $\beta$-dicarbonyl compounds. Fluorination: (a) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001. Conjugate addition: (b) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (c) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. 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.

(11) (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 ref 8b.

(12) For the preparation and use of an analogous benzoylated PTC catalyst from quinine, see: Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547. For the use of benzoylated quinine derivatives in asymmetric synthesis, see: France S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206 and references therein.

(13) We observed no improvement of the ee with **4f** ($R^1$ = 9-anthracenylmethyl, $R^1$ = Bz, X = Cl, ee (**3a**) = 53%), or varying the substituents of the benzoate aromatic ring ($R^1$ = Bn, $R^2$ = *p*-Cl-Bz/*p*-$NO_2$-Bz/*p*-$OCH_3$-Bz, X = Cl).

(14) See Supporting Information.

JA050200G