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Towards an asymmetric organocatalytic α-cyanation of β-ketoesters

Raghunath Chowdhury, Johannes Schörgenhumer, Johanna Novacek, Mario Waser *

Institute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstrasse 69, 4040 Linz, Austria

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ABSTRACT

This communication describes the first proof of concept for an asymmetric α-cyanation of β-ketoesters using a hypervalent iodine-based electrophilic cyanide-transfer reagent. A series of different organocatalysts has been investigated and it was found that the use of naturally occurring Cinchona alkaloids allows obtaining the target products in good yields and with moderate enantioselectivities up to er = 76:24 under operationally simple conditions.

Introduction

The construction of quaternary stereogenic centres is an important but challenging task.[1] The use of hypervalent iodine compounds has emerged as a powerful method for the synthesis of highly functionalized target molecules over the last years.[2] Some of the most important applications of hypervalent iodine reagents include the transfer of carbon electrophiles like aryl,[3,4] vinyl,[5] alkynyl,[6] or trifluoromethyl groups[7] to prochiral nucleophiles. However, despite the spectacular progress made using these highly electrophilic reagents, their application in asymmetric reactions is still rather challenging, especially when it comes to the synthesis of quaternary stereogenic centres.[2–7] The main challenge that arises is to ensure stereocontrol in the C–C bond forming step with a suitable asymmetric catalyst. For example, it is nowadays well accepted that the α-arylation of β-ketoesters with diaryliodonium salts proceeds via enolate O-attack to the hypervalent iodine reagent first, followed by a [2,3]-rearrangement to create the α-stereogenic centre.[3b] However, the hereby formed primary addition product is a neutral species and therefore it is difficult to control the subsequent stereo-defining rearrangement with those asymmetric catalysts that are commonly used to control prochiral enolates (e.g., asymmetric ammonium salt catalysts[8]). The groups of MacMillan and Gaunt addressed this challenge by controlling the addition of silylenolates to diaryliodonium salts using chiral Cu(I)-based catalysts.[4c,d] One approach that allows for the successful combination of hypervalent iodine reagents and asymmetric organocatalysts[9] is the use of benziodoxole derivatives as shown by the groups of Waser, Maruoka and Vesely for the asymmetric α-alkynylation of β-ketoesters[6a,b] or α-fluoro phenylsulfonyl nitromethane[6c] under phase-transfer catalysis. Hereby the primary addition product (O–I bond formation) is charged and therefore the chiral ammonium salt catalyst can control the subsequent rearrangement.[10]

Inspired by these reports and based on our own interest in asymmetric phase-transfer catalysis[11] we became interested in developing a protocol for the asymmetric α-cyanation of β-ketoesters **1** using the well-known cyano benziodoxole **2**[12–14] as an electrophilic cyanide transfer reagent (Scheme 1).

Results and discussion

Initial experiments were carried out using Cinchona alkaloid-based phase-transfer catalysts **A** for the reaction of *t*-butyl ester **1a** with cyanide **2**. During these initial investigations we obtained cyanation product **3a** accompanied by the formation of the α-brominated product **4** (see Table 1, entries 1–7 for representative results). The formation of α-halogenated products by reacting 1,3-dicarbonyl compounds and quaternary ammonium halides in the presence of hypervalent iodine reagents is a known transformation.[15] While addressing this issue by screening different organocatalysts under different conditions we became aware of a very detailed and illustrative report by Chen et al. reporting the racemic cyanation of β-ketoesters **1** and the analogous amides using **2** as the cyanide transfer reagent under base-free conditions in different solvents.[13] Interestingly, this group found that the α-hydroxy ketoester **5** is the only product under catalyst- and base-free conditions in solvents like toluene or CH_2Cl_2, whereas

* Corresponding author.
E-mail addresses: raghuch14@gmail.com (R. Chowdhury), mario.waser@jku.at (M. Waser).

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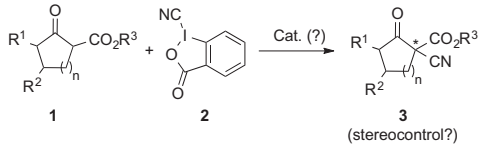
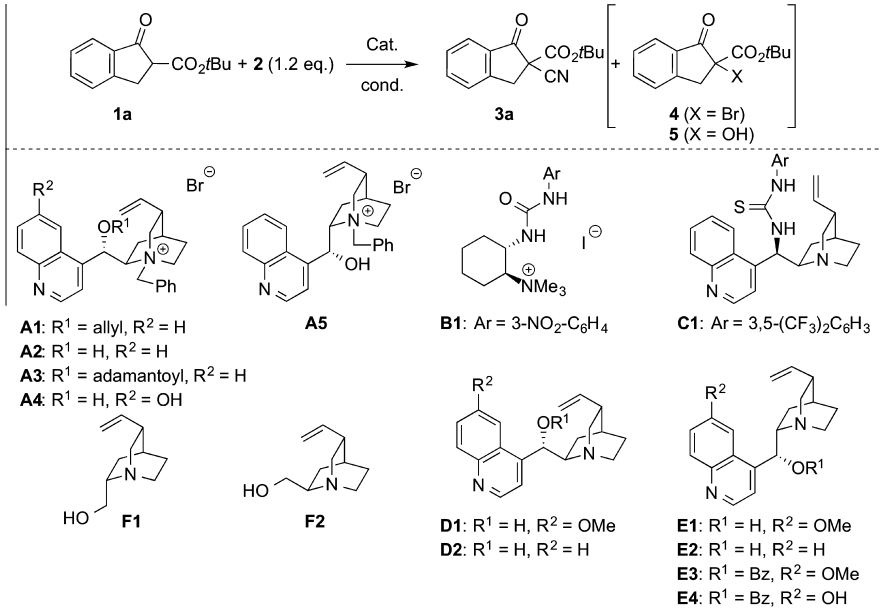


Scheme 1. Targeted asymmetric α-cyanation of ketoesters **1**.

the use of DMF allowed them to totally suppress the formation of **5**, giving the α-cyano products **3** in excellent yields of around 90% within minutes at room temperature.[13] In addition, they also observed that the presence of an achiral Cu(II) Lewis acid favours cyanation over hydroxylation to some extent when carrying out the reaction in CH_2Cl_2 (still <20% yield). Accordingly, the presence of a catalyst/additive significantly influences the product ratio in apolar solvents. This is also supported by the fact that **3a** was formed in every experiment when an organocatalyst was present but in neither case formation of **5** was observed (by ^{1}H NMR of the crude mixture).

Table 1 gives an overview of the most significant results obtained in a detailed screening of catalysts and reaction conditions. Initial experiments with phase-transfer catalysts **A** revealed that **3a** can be obtained with low enantioselectivities when using free-OH containing catalysts **A2** or **A5** and it also turned out that

Table 1
Identification of the most active organocatalyst and best-suited reaction conditions for the asymmetric synthesis of **3a**



Entry	Cat. (mol %)	Solvent	Base	*T* (°C)	*t* (h)	**3a**[a] (%)	**4**[b] (%)	er[c] (±)
1	**A1** (20%)	CH_2Cl_2	K_2CO_3 (5 equiv)	25	24[d]	58	10–15	48:52
2	**A1** (20%)	CH_2Cl_2	—	25	24	60	15–20	48:52
3	**A2** (20%)	CH_2Cl_2	—	25	24[d]	30	15–20	55:45
4	**A3** (20%)	CH_2Cl_2	—	25	24	58	15–20	50:50
5	**A4** (20%)	CH_2Cl_2	—	25	24[d]	20[b]	15–20	50:50
6	**A5** (20%)	CH_2Cl_2	—	25	24[d]	39	20 (17)[a]	42:58
7	**A5** (20%)	CH_2Cl_2	K_2CO_3 (5 equiv)	25	24[d]	47	15–20 (15)[a]	44:56
8	**B1** (10%)	CH_2Cl_2	—	25	40[d]	39	n.d.	37:63
9	**C1** (20%)	Toluene	—	25	40[d]	25	n.d.	34:66
10	**D1** (20%)	CH_2Cl_2	—	25	40	80	n.d.	64:36
11	**D2** (20%)	CH_2Cl_2	—	25	40	78	n.d.	66:34
12	**E1** (20%)	CH_2Cl_2	—	25	40	80	n.d.	38:62
13	**E2** (20%)	CH_2Cl_2	—	25	40	83	n.d.	30:70
14	**E3** (20%)	CH_2Cl_2	—	25	40	79	n.d.	50:50
15	**E4** (20%)	CH_2Cl_2	—	25	40	70	n.d.	42:58
16	**F1** (20%)	CH_2Cl_2	—	25	40[d]	66	n.d.	50:50
17	**F2** (20%)	CH_2Cl_2	—	25	40[d]	67	n.d.	47:53
18	**E2** (20%)	Toluene	—	25	40[d]	62	n.d.	33:67
19	**E2** (20%)	MTBE	—	25	40	78	n.d.	41:59
20	**E2** (20%)	$CHCl_3$	—	25	40	70[e]	n.d.	26:74
21	**E2** (10%)	$CHCl_3$	—	25	40[d]	34	n.d.	26:74
22	**E2** (5%)	$CHCl_3$	—	25	40[d]	32	n.d.	34:66
23	**E2** (40%)	$CHCl_3$	—	25	40	85	n.d.	30:70
24	**E2** (20%)	$CHCl_3$	—	0	72[d]	52	n.d.	25:75
25	**E2** (20%)	$CHCl_3$	—	40	40	57	n.d.	27:73

[a] Isolated yield.
[b] Determined by ^{1}H NMR of the crude reaction product.
[c] Determined by HPLC using a chiral stationary phase.
[d] Less than 90% conversion of **1a**.
[e] Using 2 equiv of **2** gave **3a** in 75% yield and the same enantioselectivity.