Enantioselective Iron-Catalyzed Azidation of β-Keto Esters and Oxindoles

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S *Supporting Information*

ABSTRACT: The first example of Fe-catalyzed enantio-selective azidations of β-keto esters and oxindoles using a readily available N_3-transfer reagent is reported. A number of α-azido-β-keto esters were obtained with up to 93% ee, and this methodology also generates 3-substitued 3-azidooxindoles with high enantioselectivities (up to 94%).
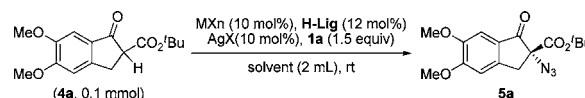
Organic azides are valuable intermediates in organic synthesis, in particular as powerful precursors for a wide range of nitrogen-containing synthetic targets.[1] During the past two decades, their utility has expanded dramatically in medicine, biology, and materials sciences.[1,2] Despite the extensive studies and significant advances in this field, the catalytic stereoselective introduction of an azido group into organic compounds remains comparatively rare.[3,4]

α-Azido-β-keto esters and 3-azidooxindoles are attractive targets because they are transformed smoothly into the corresponding amino derivatives.[5,6] However, except for several non-enantioselective syntheses,[7,8] only Shibatomi and co-workers have reported the stereospecific S_N2 substitution of optically active α-chloro-β-keto esters to generate the corresponding enantiopure α-azido-β-keto esters.[9] To the best of our knowledge, the direct catalytic asymmetric azidation of β-keto esters and oxindoles remains unexplored. On the other hand, efficient and direct stereoselective C—N bond formation is an attractive topic in organic synthesis, and only a few compounds such as azodicarboxylates[10] and nitroso derivatives[11,12] have been used as *electrophilic* sources of nitrogen. Exploring other electrophilic nitrogen sources is still a challenge.

We recently developed a class of chiral pincer ligands ("boxmi" ligands, **2**)[13] that were used, inter alia, in the asymmetric Cu-catalyzed trifluoromethylation of β-keto esters.[13c] This reaction employed 3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni's reagent)[14] as a trifluoromethylating agent. In this work, we exploited a similar strategy to achieve highly enantioselective Fe-catalyzed azidation of β-keto esters and oxindoles using the T-shaped iodine(III) compound **1a**[15] as an azido-transfer reagent.
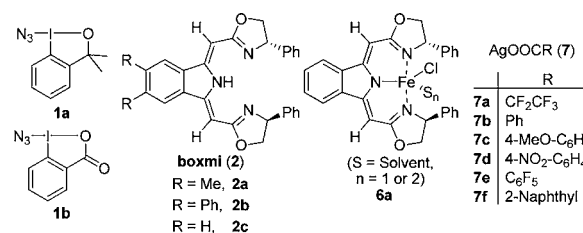
We began by using the reaction of β-keto ester **4a** with **1a** as a model reaction to investigate different kinds of metal salts [see the Supporting Information (SI)] and found iron(II) salts to be the most suitable catalyst precursors in combination with the boxmi ligands (Table 1). Various iron salts were tested in the reaction, and iron(II) propionate, $Fe(OOCEt)_2$ (**3**), was found to be optimal (entries 1–5). The choice of solvent markedly

Table 1. Optimization of the Azidation of 4a

entry	MXn	H-Lig	AgX	solvent	t (h)	yield (%)[a]	ee (%)[b]
1	Fe(OAc)₂	2a	–	CH₂Cl₂	36	87	35
2	Fe(ClO₄)₂·xH₂O[c]	2a	–	CH₂Cl₂	6	90	15
3	Fe(BF₄)₂·6H₂O	2a	–	CH₂Cl₂	24	88	11
4	Fe(OTf)₂	2a	–	CH₂Cl₂	72	76	55
5	Fe(OOCEt)₂ (3)	2a	–	CH₂Cl₂	72	80	66
6	3	2a	–	THF	48	85	76
7	3	2a	–	toluene	72	53	44
8	3	2a	–	Et₂O	72	86	81
9	3	2b	–	Et₂O	72	56	69
10	3	2c	–	Et₂O	72	86	83
11	6a	–	–	Et₂O	72	61	66
12	6a	–	7a	Et₂O	48	86	53
13	6a	–	7b	Et₂O	72	85	91
14	6a	–	7c	Et₂O	72	73	90
15	6a	–	7d	Et₂O	48	87	93
16	6a	–	7e	Et₂O	48	88	86
17	6a	–	7f	Et₂O	72	75	90
18[d]	6a	–	7d	Et₂O	72	15	53

[a]Isolated yields. [b]Determined by HPLC analysis. [c]x is defined to be 6. [d]**1b** was used instead of **1a**.

influenced both the yield and enantioselectivity, and the use of diethyl ether generated the product in 86% yield with 81% ee (entries 5–8). Further screening of ligands showed that ligand **2c** slightly improved the ee (entries 8–10).

Notably, we observed that iron(II) carboxylates gave rise to the highest enantioselectivities, prompting us to examine the effect of different carboxylate counterions in the reaction. First, the isolated Fe complex **6a** catalyzed the reaction to afford the

product with 66% ee (entry 11). Next, we exchanged the anionic ligand of the catalyst in situ by mixing equimolar amounts of **6a** and silver carboxylate. Screening of a series of silver salts showed that silver arylcarboxylates gave better ee values. Moreover, using silver benzoates with an electron-withdrawing group (**7d** and **7e**) shortened the reaction time to 48 h, and silver 4-nitrobenzoate (**7d**) improved the ee to 93% (entries 12−17). Finally, using the alternative azido-transfer reagent **1b** led to much lower activities (entry 18). It should be noted that these reactions are operationally convenient and can be performed without removal of silver chloride.

Although the Fe(II) catalysts employed in this study were generated in situ, Fe complexes bearing boxmi ligands **2** were readily isolable. Direct complexation of the *R,R* enantiomer of protioligand **2c** (the *S,S* enantiomer of the ligand was used in the catalyses) with Fe(OAc)$_2$ in methanol at room temperature gave the corresponding Fe(II) acetate complex **6b**. The molecular structure of **6b**(py), a pyridine adduct of **6b**, was established by X-ray diffraction (Figure 1) and revealed a strongly distorted
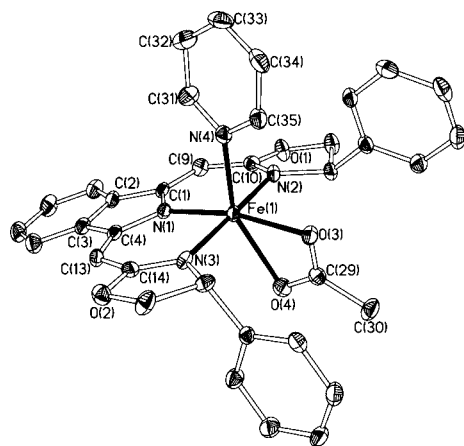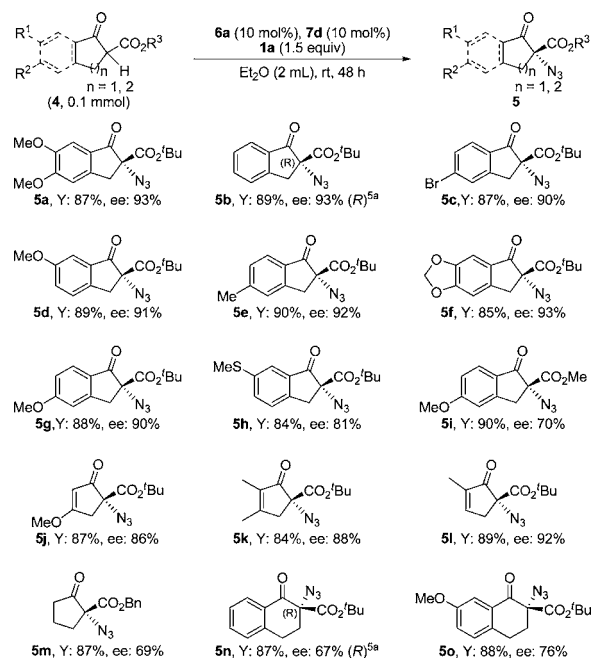

Figure 1. Structure of **6b**(py) (H atoms omitted for clarity).

octahedral coordination environment involving four N donors and an η^2-coordinated acetate. The meridional coordination mode of the pincer ligand (*R,R*)-**2c** was confirmed, with the metal in the plane spanned by the N-donor atoms [as shown by the N(2)−Fe(1)−N(3) angle of 175.0(2)°].

Under the optimized reaction conditions described above, we explored the generality of the protocol for different cyclic β-keto esters. As summarized in Scheme 1, all of the tested indanone-derived *tert*-butyl β-keto esters were converted to the corresponding products **5a**−**g** in high yields with high enantioselectivities (90−93% ee), except for the methylthio-substituted substrate, which afforded **5h** with 81% ee. It was found that a bulky ester substituent is essential for obtaining high selectivity (compare **5g** with **5i**). Three differently functionalized *tert*-butyl esters of cyclopentenone were converted to the corresponding products **5j**−**l** with high enantioselectivities. Moreover, a cyclopentanone-derived β-keto ester was also successfully employed in the process, generating **5m** with 69 ee %. Finally, the cyclic six-membered-ring derivatives **5n** and **5o** were obtained with only moderate enantioselectivities. Unfortunately, acyclic ketoesters proved to be unreactive under these reaction conditions.

The methodology described above could be extended to the azidation of 3-aryloxindoles. Oxindole **8a** was azidated with somewhat lower enantioselectivity (78% ee) compared with the

Scheme 1. Enantioselective Azidation of β-Keto Esters[a]

[a]Isolated yields and ee's determined by HPLC are shown. Absolute configurations of the products were determined on the basis of the single-crystal structure of **11** and evidenced by comparison with literature α_D values (for **5b** and **5n**).

cyclic β-keto esters under the conditions described above (Table 2, entry 1). However, with the catalyst generated in situ from 10 mol % **3** and 12 mol % **2c** and optimization of the reaction conditions, the ee value increased to 91% (entry 2).
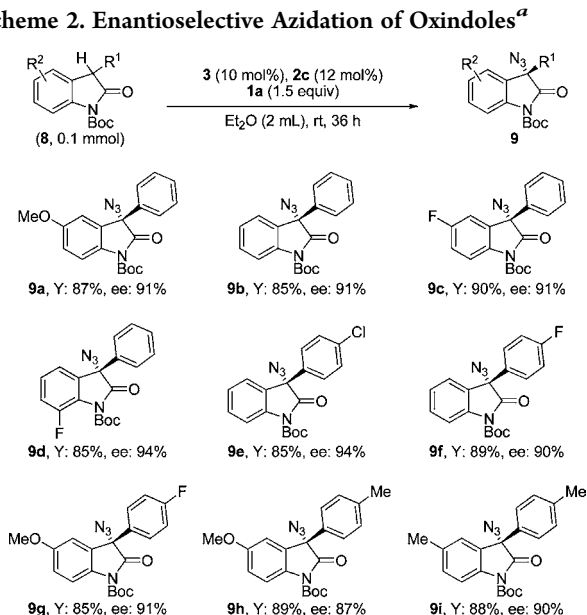
Table 2. Optimization of the Azidation of 8a

entry	MXn	H-Lig	AgX	solvent	T	t (h)	yield (%)[a]	ee (%)[b]
1	**6a**	−	**7d**	Et$_2$O	rt	36	86	78
2	**3**	**2c**	−	Et$_2$O	rt	36	87	91
3	**3**	**2c**	−	THF	rt	36	84	84
4	**3**	**2a**	−	Et$_2$O	rt	36	84	90
5	**3**	**2c**	−	Et$_2$O	0 °C	48	51	69

[a]Isolated yields. [b]Determined by HPLC analysis.
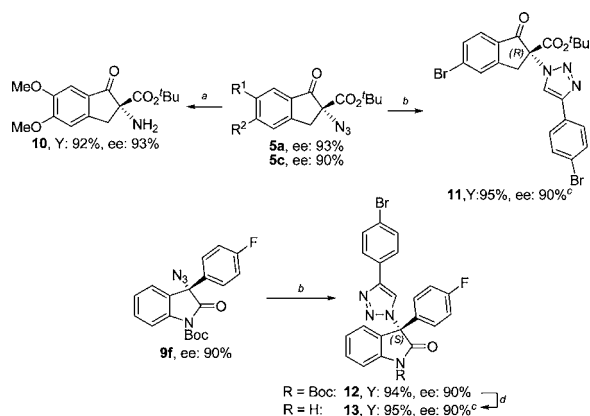
Having established the optimal reaction conditions for this type of substrate, we explored the oxindole scope of the azidation (Scheme 2). 3-Phenyloxindoles generated the corresponding products in high yields with excellent enantioselectivities (91−94% ee) regardless of the nature and the positions of the substituents on the oxindole framework (**9a**−**d**). On the other hand, the presence of an electron-donating substituent on the phenyl group at the C3 position slightly decreased the ee value (**9h** vs **9a** and **9g**).

To highlight the utility of this enantioselective azidation, we undertook further transformations of the resulting azides (Scheme 3). α-Azido ester **5a** was smoothly converted into α-amino ester **10** by Pd-catalyzed hydrogenolysis,[5a] providing a

Scheme 2. Enantioselective Azidation of Oxindoles[a]

9a, Y: 87%, ee: 91%   9b, Y: 85%, ee: 91%   9c, Y: 90%, ee: 91%

9d, Y: 85%, ee: 94%   9e, Y: 85%, ee: 94%   9f, Y: 89%, ee: 90%

9g, Y: 85%, ee: 91%   9h, Y: 89%, ee: 87%   9i, Y: 88%, ee: 90%

[a]Isolated yields and ee's determined by HPLC are shown. Absolute configurations of the products were determined on the basis of the single-crystal structure of **13**.

Scheme 3. Further Transformations of the Azide Products

10, Y: 92%, ee: 93%

5a, ee: 93%
5c, ee: 90%

11, Y: 95%, ee: 90%[c]

9f, ee: 90%

R = Boc: 12, Y: 94%, ee: 90%
R = H: 13, Y: 95%, ee: 90%[c]

[a]Conditions: H$_2$ (1 atm), Pd/BaSO$_4$ (10 mol %), MeOH, rt. [b]Conditions: 1-Bromo-4-ethynylbenzene (1.2 equiv), CuSO$_4$ (20 mol %), TBTA (1 mol %), sodium ascorbate (0.4 equiv), [t]BuOH/H$_2$O (2:1), rt. TBTA = tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine. [c]The absolute configuration was determined by X-ray structure analysis. [d]Conditions: CF$_3$COOH (5 equiv), CH$_2$Cl$_2$, rt.

useful method for the synthesis of highly substituted α-amino acid derivatives. On the other hand, the Cu-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) "click" reaction, which has been established as a powerful coupling technology,[2e,j] was used to transform α-azido ester **5c** into the corresponding triazole **11** in high yield.[7b]

The absolute configuration of the optically active **11** was established to be R by single-crystal X-ray structure analysis (Figure 2). On this basis, we determined the absolute configurations of α-azido esters **5**. Furthermore, 3-azidooxindole **9f** also generated triazole **12** in 94% yield; subsequent removal of the Boc group by treatment with trifluoroacetic acid afforded the corresponding product **13**, for which an X-ray diffraction study established the S configuration (see the SI). Since oxindoles are common structural motifs that are present in a variety of
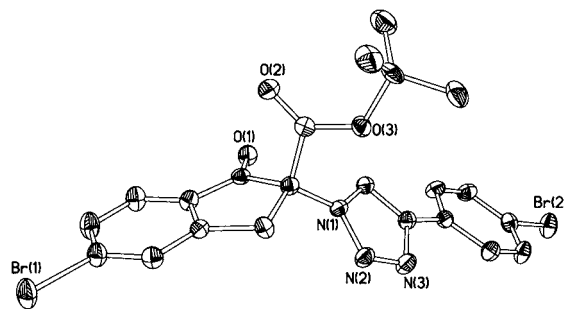

Figure 2. Structure of triazole **11** (H atoms omitted for clarity).

physiologically active molecules,[6] this approach provides a strategy for the generation of bioconjugates with enantiopure 3-substitued 3-azidooxindoles.[2f,g,k]

In conclusion, by employing the boxmi system as stereo-directing ligand, we have developed an efficient protocol for enantioselective Fe-catalyzed azidation of cyclic β-keto esters and 3-aryloxindoles using a readily available and stable azidoiodinane as an N$_3$-transfer reagent. Cyclic β-keto esters were converted to the corresponding products in high yields with up to 93% ee catalyzed by the combination of an iron(II) chlorido complex and silver carboxylate. 3-Azido-3-aryloxindoles were obtained with up to 94% ee using the catalyst prepared from iron(II) propionate and the ligand in situ. Further studies of synthetic applications of this transformation as well as the reaction mechanism are underway in our laboratory.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Methods, additional data, and CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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