Organic LETTERS

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Enantioselective Steglich Rearrangement of Oxindole Derivatives by Easily Accessible Chiral *N,N*-4-(Dimethylamino)pyridine Derivatives

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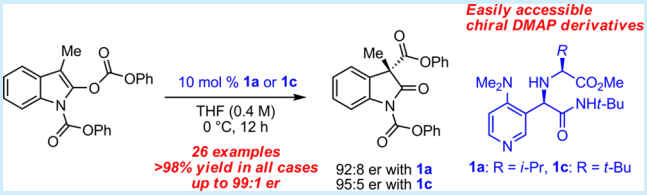
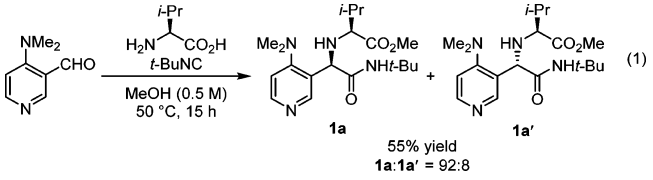
Supporting Information

ABSTRACT: Chiral *N,N*-4-(dimethylamino)pyridine (DMAP) derivatives, which can be readily prepared by the Ugi multicomponent reaction in a one-pot manner, have been efficiently applied to the enantioselective Steglich rearrangement of oxindole derivatives to give the desired products bearing a quaternary carbon center in high yield (>98% yield) and with high enantioselectivity (up to 99:1 er).



Over the past two decades, the development of chiral nucleophilic catalysts has become one of the most important areas in organic synthesis.[1] Chiral catalysts with DMAP or 4-pyrrolidinopyridine (PPY) scaffolds are widely studied in response to pioneering studies by Vedejs[2] and Fu,[3] particularly with regard to their application to various enantioselective transformations, such as the kinetic resolution of racemic alcohols[4] or amines,[5] desymmetrization of *meso*-compounds,[6] Steglich rearrangements,[7] and many others. However, most chiral DMAP and PPY derivatives have required a longer linear synthetic route as well as the optical resolution of a racemic intermediate or the final catalyst form.[1e] Thus, chiral DMAP derivatives that can be easily synthesized from a readily available chiral source in short steps (<5 steps) without cumbersome operations (e.g., optical resolution or HPLC separation) are highly attractive. Very recently, we developed a method for the synthesis of chiral DMAP derivatives starting from an α-amino acid[8,9] as a chiral source using a diastereoselective Ugi multicomponent reaction, and the protocol allowed us to access a variety of chiral catalysts in a one-step and one-pot manner.[10] For example, an L-valine-based chiral DMAP derivative was synthesized in 55% yield as a mixture of two diastereomers (**1a**/**1a**′ = 92:8, eq 1) and could be applied



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to the kinetic resolution of secondary alcohols.[11] To the best of our knowledge, this is the first example in which chiral DMAP derivatives were synthesized by a multicomponent reaction in a one-step procedure and then applied to an enantioselective acylation reaction. However, the reaction with the minor diastereomer of the Ugi product **1a**′ showed a higher selectivity factor (*s* factor) than that with the major diastereomer **1a** under the optimal conditions. Application of the major diastereomer **1a** to other important classes of enantioselective transformations is of particular interest. As a result of our extensive screening of acyl-transfer reactions with **1a**, we found that **1a** showed high catalytic activity and enantioselectivity in the Steglich rearrangement[12] of *O*-acylated oxindole derivatives. In this paper, we report the details of the optimization of the reaction conditions with **1a**, the substrate scope, and computational studies to elucidate the reaction mechanism.

Initially, the Steglich rearrangement of oxindole **2a** was carried out in the presence of 10 mol % of diastereomerically and enantiomerically pure catalyst **1a** with an L-valine scaffold, a major diastereomer of the Ugi product, in various solvents at 0 °C for 12 h (Table 1). The reaction in common organic solvents (0.1 M) afforded the product **3a** in low to moderate conversion (10−79% conv) with an acceptable enantioselectivity (89:11 to 92:8 er, entries 1−7). The use of a protic solvent, *tert*-amyl alcohol, significantly suppressed the reaction efficiency (entry 7). According to the solvent screening, the reaction in THF was found to be optimal at 0 °C with respect to both product conversion and enantioselectivity (78% conv; 92:8 er; entry 3).

Received: July 21, 2015

DOI: 10.1021/acs.orglett.5b02089
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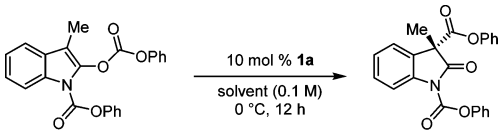
Table 1. Screening of the Solvent and Reaction Temperature[a]



2a 3a

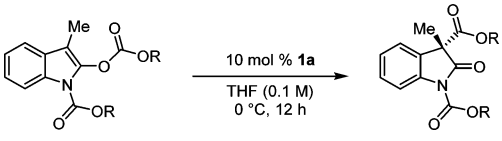
entry	solvent	temp (°C)	conv[b] (%)	er of 3a[c]
1	CH_2Cl_2	0	54	92:8
2	toluene	0	70	91:9
3	THF	0	78	92:8
4	Et_2O	0	79	91:9
5	*i*-Pr_2O	0	71	89:11
6	CPME	0	73	91:9
7	*t*-amyl alcohol	0	10	92:8
8	THF	rt	>98	90:10
9	THF	−20	76	85:15

[a]Reactions were performed on a 0.1 mmol scale in solvent (0.1 M) under an argon atmosphere. [b]Conversions were determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c]Enantioselectivities were determined by HPLC analysis.

The effect of the reaction temperature was also examined (entries 8 and 9). At room temperature, the reaction proceeded smoothly (>98% conv), but the enantioselectivity was slightly decreased (90:10 er; entry 8 vs 92:8 er; entry 3). While the same conversions (76% conv) were seen at a lower temperature of −20 °C, the enantiomeric ratio was significantly decreased compared to that at 0 °C (85:15 er; entry 9 vs 92:8 er; entry 3). According to these results, the reaction in THF (0.1 M) at 0 °C was optimal in the enantioselective Steglich rearrangement of oxindoles with catalyst **1a**.

Next, we examined the effects of carbonate and carbamate moieties on the reaction conversion and the enantioselectivity of the product (Table 2). The use of alkyl-substituted carbonates **4a**−**7a** resulted in no reaction (<2% conv) at all (entries 2−5). Benzyl-substituted carbonate **8a** slightly facilitated the transformation (10% conv to **11a**; 88:12 er; entry 6). On the other hand, aryl-substituted carbonates **9a** and **10a** were converted to

Table 2. Effects of Carbonate and Carbamate Moieties on the Reaction Conversion and Enantioselectivity[a]



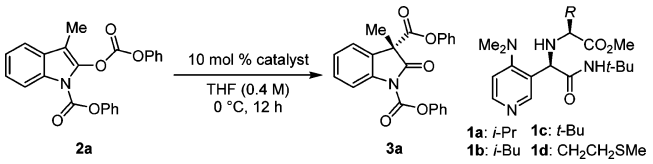
entry	R	substrate	product	conv[b] (%)	er of product[c]
1	Ph	**2a**	**3a**	78	92:8
2	Me	**4a**		<2	
3	Et	**5a**		<2	
4	*i*-Pr	**6a**		<2	
5	*i*-Bu	**7a**		<2	
6	Bn	**8a**	**11a**	10	88:12
7	4-$MeOC_6H_4$	**9a**	**12a**	50	91:9
8	4-FC_6H_4	**10a**	**13a**	>98	68:32
9[d]	Ph	**2a**	**3a**	>98	92:8

[a]Reactions were performed on a 0.1 mmol scale in THF (0.1 M) under an argon atmosphere. [b]Conversions were determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c]Enantioselectivities were determined by HPLC analysis. [d]The concentration of substrate was 0.4 M.

the corresponding products **12a** (50% conv; 91:9 er; entry 7) and **13a** (>98% conv; 68:32 er; entry 8), respectively. An electron-donating group substituted phenyl carbonate **9a** dramatically decreased the reaction conversion with an identical enantioselectivity. On the other hand, **10a** with an electron-withdrawing group resulted in moderate enantioselectivity of the product **13a** (entry 8). The reaction of **2a** at a higher concentration delivered the desired product **3a** in >98% conversion with 92:8 er after 12 h (entry 9).

To identify an L-amino acid moiety of the catalyst that could influence the enantioselectivity, the Steglich rearrangement of oxindole **2a** was carried out with 10 mol % of selected catalysts **1a**−**d** in THF (0.4 M) at 0 °C for 12 h (Table 3). The reaction

Table 3. Screening of Selected Catalysts[a]



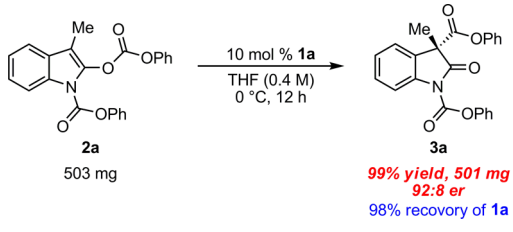
2a 3a

entry	catalyst	conv[b] (%)	er of 3a[c]
1	**1a**	>98	92:8
2[d]	**1a** + **1a′**	>98	80:20
3	**1b**	>98	91:9
4	**1c**	>98	95:5
5	**1d**	>98	91:9

[a]Reactions were performed on a 0.1 mmol scale in THF (0.4 M) under an argon atmosphere. [b]Conversions were determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c]Enantioselectivities were determined by HPLC analysis. [d]Diastereomeric mixture of catalyst (**1a** + **1a′**, 92:8 dr) was used in the reaction.

with a mixture of the diastereomers **1a** and **1a′** (92:8 dr) decreased the enantioselectivity of **3a** compared to that with diastereomerically pure **1a** (80:20 er; entry 2 vs 92:8 er; entry 1). Compound **1a′** should act as a pseudoenantiomer of **1a**, and diastereomerically pure catalyst should be used in the reaction. The sense of enantioselectivity for the reaction may mainly be determined by the absolute configuration of the stereogenic center immediately adjacent to the DMAP skeleton. The L-isoleucine-derived catalyst **1b** slightly decreased the enantioselectivity of **3a** (91:9 er, entry 3), whereas the more sterically demanding L-*tert*-leucine-derived catalyst **1c** afforded the desired product **3a** in 95:5 er (entry 4). L-Methionine-based DMAP derivative **1d** was slightly inferior to catalyst **1a** and **1c** in terms of enantioselectivity (91:9 er, entry 5). According to these results, we selected **1c** as well as **1a** containing inexpensive L-valine as optimal catalyst candidates.[13]

Under the optimal conditions, we carried out a preparative-scale reaction and tested the recovery of catalyst **1a**. As shown in eq 2, the reaction of **2a** (502.7 mg, 1.3 mmol) with catalyst **1a**



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DOI: 10.1021/acs.orglett.5b02089
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proceeded smoothly to afford the desired product in >98% yield with 92:8 er, and **1a** was recovered in 98% yield. Furthermore, the recovered catalyst **1a** could catalyze another batch of reaction (0.2 mmol scale) without any loss of catalytic activity and enantioselectivity (see the Supporting Information for details), indicating the robust nature of **1a**.

The enantioselective Steglich rearrangement of an array of substrates **2b–n** was carried out with 10 mol % **1a** or **1c** in THF (0.4 M) at 0 °C for 12 h (Figure 1). 3-Alkyl-, allyl-, and propargyl-

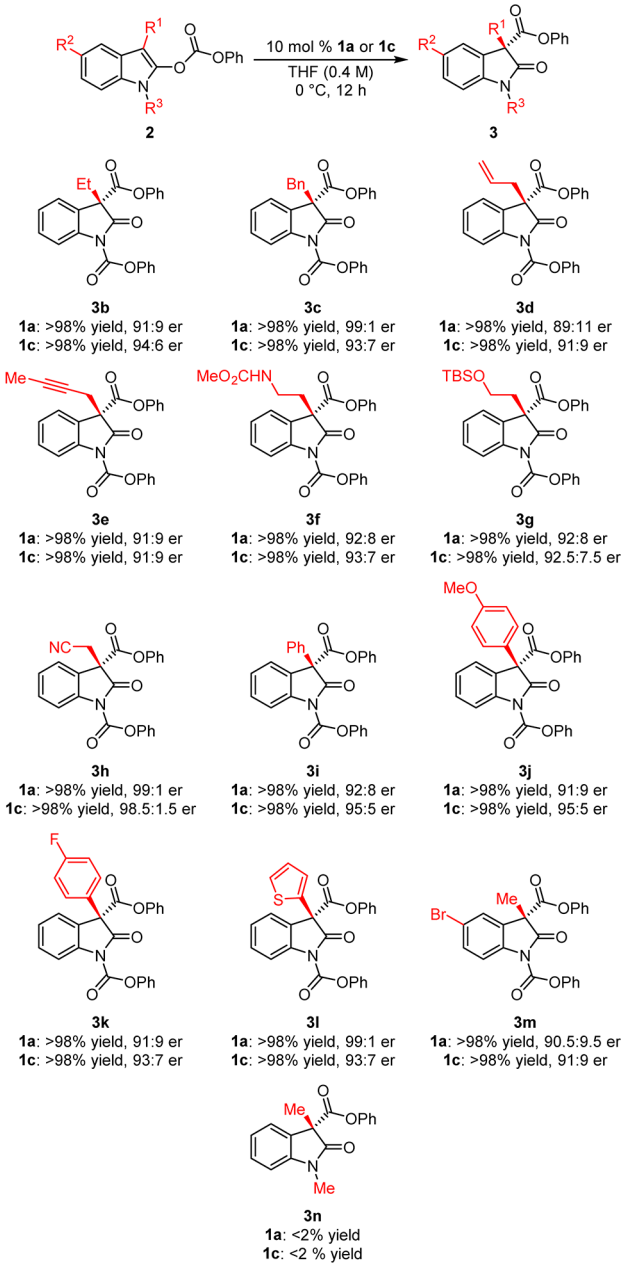

Figure 1. Enantioselective Steglich rearrangement of various *O*-acylated oxindole derivatives with catalyst **1a** or **1c**.

substituted *O*-acylated oxindole derivatives **3b–e** were efficiently obtained in >98% yields with moderate to excellent enantioselectivities (up to 99:1 er). The reaction of 3-alkyl substrates having a functional group ($-CH_2CH_2NHCO_2Me$, $-CH_2CH_2OTBS$, or $-CH_2CN$) **2f–h** also proceeded efficiently, and the desired products **3f–h** were obtained in >98% yield with 92:8 to 99:1 er. In addition, the reaction of 3-aromatic- or 3-heteroaromatic-substituted oxindole derivatives **2i–l** gave good to excellent enantioselectivity. Catalysts **1a** and **1c** could be applied to not only 3-alkyl-substituted oxindoles but also to a 3-aromatic- or 3-heteroaromatic-substituted substrate with good to high enantioselectivity. Substrate **2m** with a bromo substituent at the benzene ring could be used in this reaction with an acceptable level of enantioselectivity (90.5:9.5 er with catalyst **1a**, and 91:9 er with catalyst **1c**). However, the reaction of *O*-acylated oxindole derivatives with an *N*-Me protecting group **2n** did not proceed at all, suggesting that an *N*-acyl moiety is required for the reaction. According to these results, catalysts **1a** and **1c** can be applied to a wide range of substrates including 3-alkyl-, -allyl-, and -propargyl-substituted oxindoles. These findings allow us to access various synthetically valuable 3,3′-disubstituted oxindole derivatives with a quaternary stereogenic center.

The Steglich rearrangement of substrate **2c** using catalyst **1a** is believed to proceed through the formation of ion-pair intermediate, pyridinium cation **I** and enolate **II** (Figure 2),[7b,14] followed by C–C bond formation to give product **3c**.

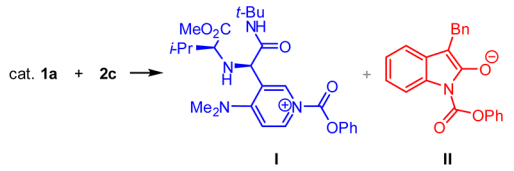

Figure 2. Ion-pair intermediate in the Steglich rearrangement.

The transition states of C–C bond formation for the reaction system of **2c** using **1a** were calculated at the B3LYP/6-31G(d) level. We identified 12 structures as candidates for the transition states: six structures, TS^S series, gave an *S*-product and six, TS^R series, gave an *R*-product (see the Supporting Information). Among the possible transition structures, $Ts^S(CO^A\_C{=}CO)$ and $Ts^R(CO^A\_C{=}CO)$ showed the lowest energies in the TS^S and TS^R series, respectively (Figure 3).

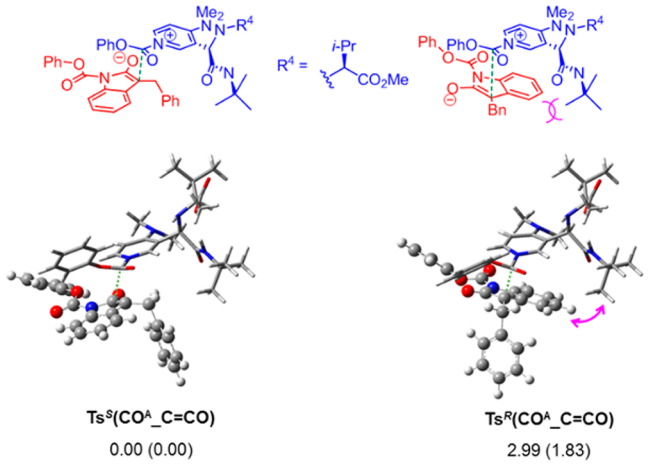

Figure 3. Schematic representation models and 3D models of energetically favorable $Ts^S(CO^A\_C{=}CO)$ and $Ts^R(CO^A\_C{=}CO)$. The ion-pair structures of **I** and **II** in the 3D models are represented as "tube" and "ball & bond type" models, respectively. The relative free energies (kcal/mol) of single-point energy calculations with the SCRF method based on CPCM (THF) are shown, and values in parentheses are the relative energies (kcal/mol).

DOI: 10.1021/acs.orglett.5b02089
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Single-point energy calculations with the self-consistent reaction field (SCRF) calculation based on the polarizable continuum model (CPCM, THF) were carried out at the 6-311+g** level for both cases. The gap in relative energies between the two transition states was $\Delta G = 2.99$ kcal/mol ($\Delta E =$ 1.83 kcal/mol), which is consistent with the experimental enantioselectivity of **3c** using **1a** (99:1 er). In both TS structures, the enolate fragment (C═C−O$^-$) in **II** and the reactive carbonyl group in **I** are oriented in an *anti*-conformation (Figure 3). In the case of $\mathbf{Ts^R(CO^A\_C{=}CO)}$, a phenylene group of **II** is located close to the *t*-Bu group of the catalyst, which would cause destabilization. In contrast, the *tert*-butyl group of the catalyst in $\mathbf{Ts^S(CO^A\_C{=}CO)}$ is far from an adjacent group (Bn) of **II**. We could not obtain any evidence of positive interaction (e.g., cation−π) in these transition states.

In conclusion, we have developed an enantioselective Steglich rearrangement of *O*-acylated oxindoles to give the desired products possessing a quaternary stereogenic center in >98% yield with up to 99:1 er. The reaction proceeded smoothly in the presence of 10 mol % of **1a** or **1c**, which can be readily prepared by the diastereoselective Ugi reaction in a one-step and one-pot manner. Such easy-to-prepare catalysts in the enantioselective Steglich rearrangement of *O*-acylated oxindole derivatives have not been reported previously. The application of such a catalyst scaffold to other important classes of enantioselective transformations is now underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02089.

Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was partially supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT (Japan). The authors gratefully thank the Division of Instrumental Analysis, Department of Instrumental Analysis & Cryogenics, Advanced Science Research Center, Okayama University, for NMR and high-resolution mass spectrometry measurements (FAB).

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DOI: 10.1021/acs.orglett.5b02089
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