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# AcOLeDMAP and BnOLeDMAP: Conformationally Restricted Nucleophilic Catalysts for Enantioselective Rearrangement of Indolyl Acetates and Carbonates

Trisha A. Duffey, Scott A. Shaw, and Edwin Vedejs*

*Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109*

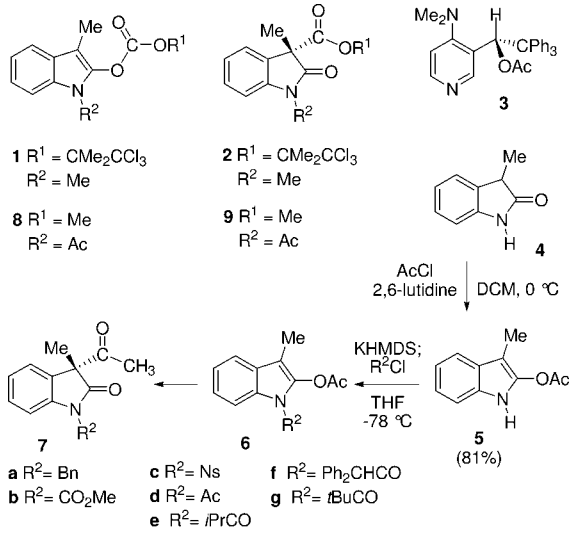
Received July 16, 2008; E-mail: edved@umich.edu

The catalytic asymmetric synthesis of all-carbon oxindole quaternary centers has been a difficult challenge. Significant advances have been described using phase-transfer,[1] transition metal,[2−5] and chiral nucleophilic catalysts.[6−9] Examples of the latter process include the highly enantioselective rearrangement of indolyl carbonates **1** to the oxindoles **2** catalyzed by planar-chiral pyridines (2 days, 35 °C, 10 mol% catalyst).[6] Catalyst **3** (TADMAP) also promoted the rearrangement, but a marginal enantioselectivity/reactivity profile at 10% catalyst loading discouraged detailed optimization.[7] Herein, we report a dramatic substitution effect that solves the reactivity problem. We also describe the development of practical new catalysts featuring a chiral side chain that prefers a uniquely advantageous conformation. These advances enable enantioselective acyl and carboxyl migration in the oxindole series.

Preparation of versatile substrates related to **1** from *N*-protected oxindoles was challenging due to competing reaction at O and C, but kinetic *O*-acetylation of oxindole **4** with acetyl chloride/2,6-lutidine afforded enol acetate **5** in acceptable 81% yield.[10] Deprotonation of **5** followed by trapping with reactive electrophiles then gave differentially protected indolyl acetates **6** for initial evaluation. Upon catalysis with DMAP (3%), the *N*-benzyl (**6a**) or *N*-alkoxcarbonyl (**6b**) derivatives rearranged slowly to the oxindoles *rac*-**7** (89% and 78% conversion, 5 h, rt) (Scheme 1). On the other hand, the *N*-nosyl (**6c**) or *N*-acyl (**6d**−**f**; **8**) analogues rearranged completely within 20 min (>95%) while **6g** rearranged to the extent of 84%. Therefore, reactivity increases when more electron-withdrawing substituents are placed at indole N.

When **3** was used to catalyze the rearrangement of indolyl acetate **6d** to **7d**, much improved reactivity was observed (98% isolated after 3 h, rt; 10% catalyst), but the 20% ee prompted a re-evaluation of the catalyst. One concern was that synthesis of enantiopure **3** requires classical resolution. Also the trityl group offers few options for catalyst modification short of repeating the entire five-step synthesis/resolution sequence.

***Scheme 1***

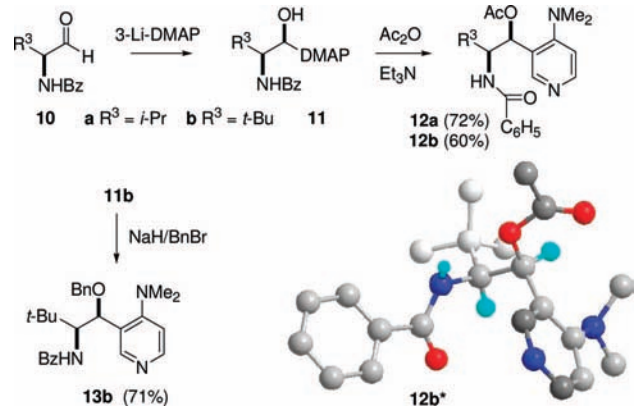



Accordingly, a new family of catalysts was designed that incorporates both electronic and steric factors expected to favor a specific side chain conformer. Thus, (*S*)-*N*-benzoylvalinol[11] was oxidized to aldehyde **10a** and 3-Li-DMAP (from the bromide)[7] was added to afford the alcohol **11a**. Subsequent acylation yielded **12a** (AcOVaDMAP, 6:1 dr, 72% from **10a**, Scheme 2). A similar route from (*S*)-*tert*-leucinol afforded **12b** (AcOLeDMAP, >98:2 dr; 60% from **10b**). Because diastereomer separation was not necessary with **12b**, this catalyst was used for most of the optimization studies. A third catalyst **13b** (BnOLeDMAP) was prepared by *O*-benzylation of isolated **11**. The stereochemistry and the expected geometry of **12** and **13** (*anti* DMAP and *t*Bu groups; *gauche* OAc and NHBz substituents) were confirmed by X-ray crystallography as shown in **12b*** and by $J_{1,2}$ < 1 Hz for the OCHCHNBz protons of **12b** and **13b**. This points to a strong preference for a well-defined catalyst geometry having the benzamido substituent near the catalytic site at the nucleophilic pyridine nitrogen.

Catalyst **12b** effected rearrangement of the *N*-acetyl substrate **6d** to **7d** with 61% ee (THF, rt). *N*-nosyl indole **6c** gave similar results (58% ee), while the *N*-isobutyryl indole **6e** rearranged with increased selectivity (77% ee). Reactivity dropped significantly with the *N*-pivalyl analogue **6g**, but the *N*-diphenylacetyl (*N*-DPA) indole **6f** gave good enantioselectivity in THF (89% ee) without impeding the reaction. Optimal 92% ee was obtained in ethyl acetate at 0 °C, although other common solvents also gave good results.

Preparation of **6f** according to Scheme 1 afforded modest yields, so a new route to *N*-DPA indolyl esters was developed. Heating **4** in neat $Ph_2CHCOCl$ (1.5 equiv) yielded **14** (85%), and reaction with AcCl/$Et_3N$ afforded the easily purified, crystalline indolyl acetate **15a** as well as ca. 5% of the *C*-acetylated isomer (Scheme 3). Various indolyl acetates prepared in this way were then subjected to catalysis by **12b** (Table 1). Unbranched alkyl groups at the 3-position promoted rearrangement to **16** with good selectivity and reactivity (entries 1−6). A branched alkyl group (*i*-Pr) decreased the rate but gave oxindole **16f** with 94% ee, while the more reactive 3-phenyl derivative **15g** rearranged with lower selectivity (entry 8).[12] The 5-bromoindolyl acetate **17** reacted completely within 20 min, and the purified major

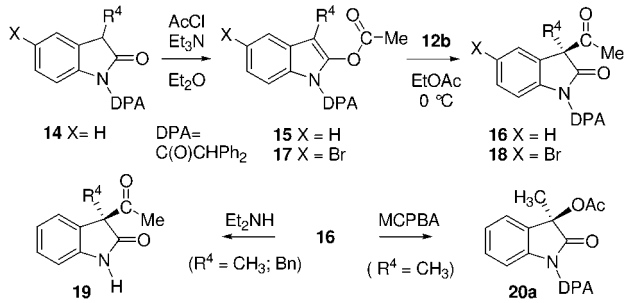
***Scheme 2***





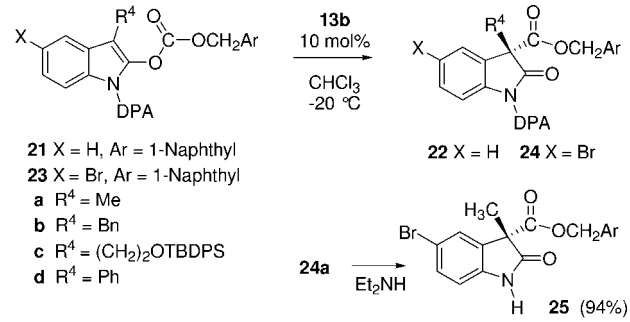

10.1021/ja805541u CCC: $40.75 

***Scheme 3***




**14** X= H **15** X = H **16** X = H
**17** X = Br **18** X = Br
**19** **20a**

***Scheme 4***




**21** X = H, Ar = 1-Naphthyl
**23** X = Br, Ar = 1-Naphthyl
**a** $R^4$ = Me
**b** $R^4$ = Bn
**c** $R^4$ = $(CH_2)_2$OTBDPS
**d** $R^4$ = Ph

**22** X = H **24** X = Br
**25** (94%)

oxindole **18** was found to have the (*S*) configuration by X-ray crystallography (anomalous dispersion). Since the oxindoles **16** and **18** have the same sign of optical rotation and similar chromophores, and also have similar relative mobility for major vs minor enantiomers on chiral hplc supports, **16a**−**g** and **18** were assigned the same configuration by analogy.

Using 1 mol% of **12b**, **15a** rearranged on gram scale within 24 h (entry 2), and recrystallization upgraded the resulting **16a** to 99% ee. The valine derived catalyst **12a** (AcOVaDMAP) was also effective (**16a**: 88% yield, 90% ee). If desired, the *N*-DPA products **16** can be deprotected to the N−H oxindoles **19**. Strong base[13] or primary amines removed DPA as well as acetyl groups in **16**, but diethyl amine selectively cleaved DPA to give the parent oxindole (**19a**, 75%; **19c** 65%). Retention of configuration was confirmed in the latter case (94% ee). To further illustrate synthetic potential, **16a** (88% ee) was converted into **20a** (73% yield; 87% ee) under Baeyer−Villiger conditions (MCPBA/$NaHCO_3$, $CH_2Cl_2$/reflux).

Catalyst **12b** was also evaluated with the indolyl carbonate substrates. Rearrangement from **8** to **9** occurred readily (5 h, rt), but enantioselectivity was low (4% ee). The reason became clear when NMR/MS assay of recovered catalyst revealed clean conversion of **12b** to an oxazoline resulting from loss of the *O*-acetyl group.[14] Stable **13b** catalyzed the conversion from **8** to **9** with modest 33% ee, but good enantioselectivity was achieved by optimizing substituents. Thus, the *N*-DPA indolyl carbonates **21** or **23** (available from 1-naphthylmethyl chloroformate) were converted into oxindoles **22** or **24** with 90−94% ee using **13b** in several representative examples (entries 10−14; $CHCl_3$, −20 °C). Remarkably, these reactions afforded oxindoles having the *opposite* configuration compared to **16** or **18** obtained using catalyst **12b** according to X-ray crystallography data for **25**, obtained in 94% yield by treatment of **24a** with diethyl amine (Scheme 4).[15]

In summary, carboxyl and acetyl migration of indolyl esters is strongly accelerated by *N*-acyl groups. Easily accessible AcOLeDMAP (**12b**) and BnOLeDMAP (**13b**) are the most practical and versatile nucleophilic catalysts reported to date for enantioselective rearrangement of indolyl acetates and carbonates to oxindoles containing chiral quaternary carbon. The interplay between migrating group substituents and catalyst modifications at the benzylic oxygen has striking consequences, as illustrated by the complementary enantiofacial selectivity for **13b** with **21/23** vs **12b** with **15/17**.[16] Furthermore, the catalyst design highlights a conformationally restricted side chain that may have other uses in situations where convergent functionality in a chirotopic environment is required.

Table 1

| entry | indole | $R^4$ | time | product | ee |
|---|---|---|---|---|---|
| 1 | **15a** | Me | 2 h[a] | **16a** 94% | 92% |
| 2 | **15a** | ” | 24 h[b] | **16a** 99% | 92% |
| 3 | **15b** | Et | 2.5 h[a] | **16b** 98% | 91% |
| 4 | **15c** | Bn | 3 h[a] | **16c** 96% | 94%[c] |
| 5 | **15d** | $(CH_2)_2$OTBDPS | 3 h[a] | **16d** 94% | 91% |
| 6 | **15e** | Allyl | 2.5 h[a] | **16e** 98% | 86% |
| 7 | **15f** | *i*-Pr | 42 h[a] | **16f** 82% | 94% |
| 8 | **15g** | Ph | 2 h[a] | **16g** 98% | 66% |
| 9 | **17** | Me | 0.33 h[a] | **18** 95% | 85% |
| 10 | **21a** | Me | 23 h[d] | **22a** 91% | 90% |
| 11 | **21b** | Bn | 23 h[d] | **22b** 98% | 92% |
| 12 | **21c** | $(CH_2)_2$OTBDPS | 23 h[d] | **22c** 99% | 94% |
| 13 | **21d** | Ph | 2 h[d,e] | **22d** 98% | 91% |
| 14 | **23a** | Me | 5 h[d,e] | **24a** 90% | 90% |

[a] 10 mol % **12b**, 0.2 M, EtOAc, 0 °C. [b] 1 mol % **12b**. [c] Ee of deprotected NH oxindole. [d] 10 mol% **13b**, 0.8M, $CHCl_3$, −20 °C. [e] 0.2 M.

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

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(15) Oxindole **22a** has the same configuration as **24a** according to correlation by debromination of **24a** with $Bu_3SnH$. Oxindoles **22** and **24a** have the opposite sense of optical rotation compared to **16** and **18**. The chemical correlation of **22a** with **24a** also supports the analogies used to assign the absolute configurations of **16**.
(16) Using **13b** in place of **12b** for Table 2, entry 1, affords the same major enantiomer of **16a** (77% ee; E. McGreevy, unpublished results).

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