ORGANIC LETTERS

2012
Vol. 14, No. 23
5968–5971

Assembly of Spirooxindole Derivatives via Organocatalytic Iminium-Enamine Cascade Reactions

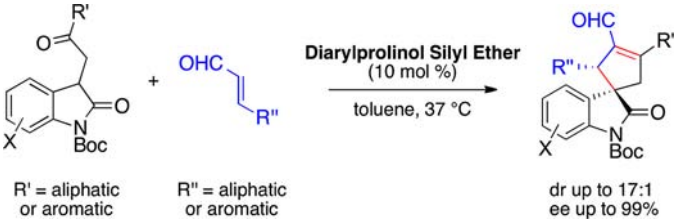
Klaus Albertshofer, Kimberly E. Anderson, and Carlos F. Barbas III*

The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

carlos@scripps.edu

Received October 18, 2012

ABSTRACT



The assembly of complex spirocyclopentaneoxindoles via a novel organocatalytic iminium-enamine cascade process is reported. Reactions between 3-substituted oxindoles and α,β-unsaturated aldehydes catalyzed by second generation prolinol ethers provided the desired products in high yield with excellent levels of enantioselectivity in a single step.

Highly substituted carbocyclic spirooxindole units are often found in natural products or synthetic molecules of pharmaceutical interest (Figure 1).[1] For example, spiroindolones have potential for treatment of malaria.[2] The high density of substituents on the spirocyclic ring system, often with multiple quaternary stereocenters, makes the assembly of these complex building blocks challenging. The enantiopure construction of spirocyclopentaneoxindoles has been carried out using transition metal catalysts,[3] nucleophilic phosphine catalysts,[4] and cinchona alkaloid catalysts[5] and through cycloaddition processes.[6] Due to the promising medicinal properties of these compounds, novel methods for the diversity-oriented assembly of spirocyclopentaneoxindoles in enantiopure forms are needed.

Since the development of modern organocatalysis at the turn of this century, iminium−enamine reaction cascades

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10.1021/ol302876c
Published on Web 11/14/2012

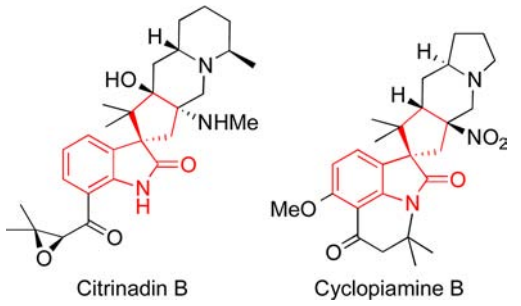

Figure 1. Naturally occurring and bioactive natural products containing the spirooxindole core structure.

have been at the center of the explosive growth in what are now more generally termed as organocascade reactions.[7] There are now numerous examples of organocascade reactions that produce stereochemically complex compounds in a single step.[8] This approach has been used successfully for the synthesis of spirocyclic oxindole derivatives.[4−6,9−11] Recently, our own laboratory disclosed the assembly of spirocyclic oxindoles via Michael−Aldol,[5a] Michael−Henry,[5d] and other organocascade strategies.[4b,6a,6f] Inspired by these studies, a novel iminium−enamine cascade reaction between 3-substituted oxindole derivatives and α,β-unsaturated aldehydes was designed (Figure 2). This strategy allowed for the construction of molecules containing two chiral centers, one of them a quaternary carbon center, in a single step.

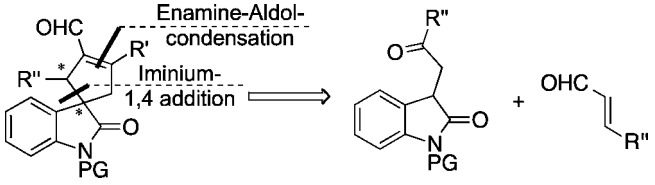

Figure 2. Retrosynthetic analysis for the construction of spirocyclo-3,3-oxindoles via an iminium−enamine cascade reaction.

Initially, a series of primary and secondary amine-containing catalysts **I**−**VI** were tested for their ability to promote a model reaction between 3-substituted oxindole **1a** and *trans*-2-butenal **2a** in dichloromethane (DCM) at 37 °C (Figure 3). Secondary amine-containing catalysts provided reaction products in higher selectivity and yield than their counterparts with primary amines. Catalysts **I**[10a] and **II**[12,13] did not promote the transformation in satisfactory yields under the evaluated conditions (Table 1, entries 1, 2). When the Takemoto-type catalyst **III**[14] was employed, spirocyclic oxindole **3a** was obtained in 15% yield and 92% enantiomeric excess (ee) (entry 3). Methoxymethylpyrrolidine **IV**, the first prolinol ether catalyst developed,[15] provided **3a** in 18% yield and 15% ee (entry 4). Use of the second generation diarylprolinol derivative **V**[16] resulted in an ee of 95%, although the yield was a moderate 20% (entry 5).

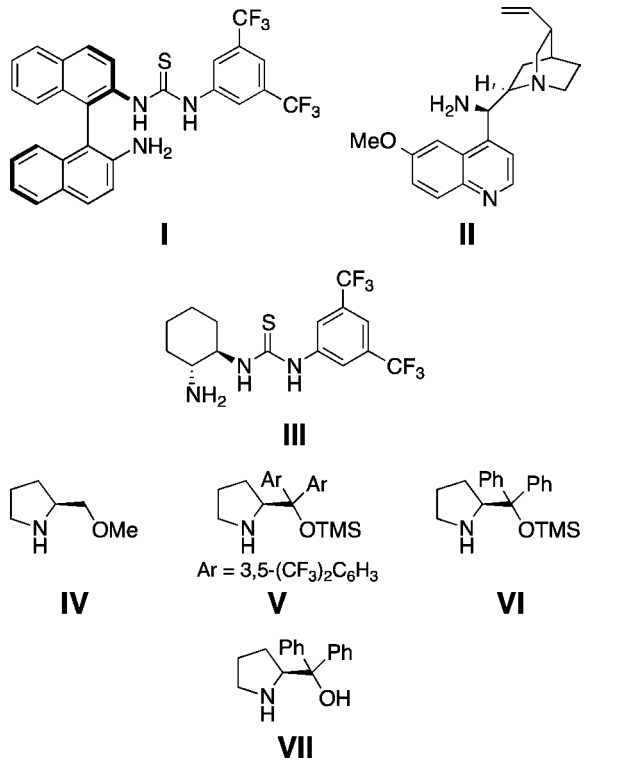

Figure 3. Organocatalysts employed in the asymmetric iminium−enamine cascade reaction.

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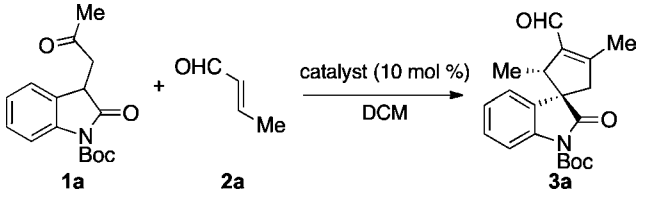
TMS-protected diphenylprolinol **VI**[16] afforded the desired product **3a** in 96% ee and 25% yield (entry 6). Unprotected diphenylprolinol **VII**[7,17] did not catalyze our model reaction, indicating the importance of a sterically bulky hydroxyl protecting group. In an attempt to improve the yield, the concentration of aldehyde **2a** was decreased incrementally from 4 to 1 equiv (entries 8–10). With decreasing amounts of enal, the formation of **3a** was favored in the presence of catalyst **VI**, leading to an improved yield of 60% with a diastereomeric ratio (dr) of 6:1 and ee of 92% (entry 10).

As catalyst **VI** was the most efficient of those tested, the effect of solvent on the model reaction in the presence of this catalyst was evaluated (see Supporting Information). Aprotic, nonpolar solvents such as toluene were optimal (Table 1, entry 11). Lowering the reaction temperature reduced the yield compared to the reaction at 37 °C (entry 12). In a final attempt to increase yield and stereoselectivity, additives were evaluated (see Supporting Information). Addition of benzoic acid afforded **3a** with 17:1 dr, 94% ee, and 90% yield (entry 13).

Table 1. Catalyst Screen and Optimization Studies[a]

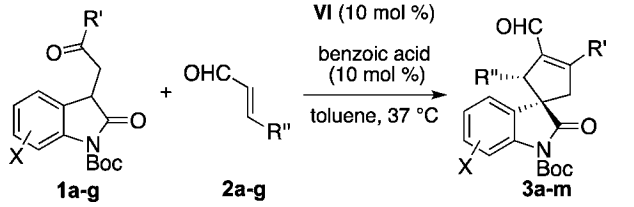


entry	catalyst	equiv of aldehyde	temp (°C)	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	**I**	4	37	<5	–	–
2	**II**	4	37	<5	–	–
3	**III**	4	37	15	n.d.	92
4	**IV**	4	37	18	n.d.	15
5	**V**	4	37	20	n.d.	95
6	**VI**	4	37	25	n.d.	96
7	**VII**	4	37	<5	n.d.	n.d.
8	**VI**	2	37	35	7:1	94
9	**VI**	1.5	37	55	8:1	93
10	**VI**	1	37	60	6:1	92
11[e]	**VI**	1	37	90	13:1	92
12[e]	**VI**	1	rt	49	14:1	89
13[e,f]	**VI**	1	37	90	17:1	94

[a] Reaction conditions unless otherwise indicated: 3-substituted oxindole (0.035 mmol, 1 equiv), aldehyde (0.144 mmol, 4 equiv), catalyst (10 mol %), DCM (140 μL, 0.25 M); no workup. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude product. [d] Determined by chiral-phase HPLC analysis. [e] Toluene (140 μL, 0.25 M) used as solvent. [f] 10 mol % benzoic acid.

The generality of the methodology developed was evaluated by screening a wide range of α,β-unsaturated aldehydes (**2a**–**g**) in the presence of 3-substituted oxindole **3a**, diarylprolinol silyl ether **VI**, benzoic acid at 37 °C. Alkyl as well as aryl substituents were tolerated on enal reactants with products obtained in excellent selectivity and yield in 24 h (Table 2). Enals with alkyl substituents such as pentyl, ethyl, and methyl reacted to afford products in diastereomeric ratios between 9:1 and 17:1 and enantiomeric ratios of 94–97% (Table 2, entries 1–3). With the least sterically hindered *trans*-2,3-butenal **2a**, the reaction yield was 91% (entry 3). α,β-Unsaturated aldehydes bearing no substituent on C-3 provided reaction product **3d** in 96% yield; however, a drop of ee to 23% was observed (entry 4). Neutral, electron-donating, and electron-withdrawing substituents on the aryl moiety of the enal had little to no effect on selectivity and yield. Products were obtained in 95% ee (99% ee after single recrystallization) and 9:1 dr and yields of 93–95% (entries 5–7).

Table 2. Scope of the Reaction[a]



entry	R′	R″	X	product	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	Me	Pent	H	**3b**	81	>9:1	96
2	Me	Et	H	**3c**	82	9:1	97
3	Me	Me	H	**3a**	91	17:1	94
4	Me	H	H	**3d**	96	–	23
5	Me	Ph	H	**3e**	95	9:1	95
6	Me	2-NO_2-Ph	H	**3f**	93	9:1	95 (99)[f]
7	Me	2-MeO-Ph	H	**3g**	95	9:1	95
9	Me	Me	5-Me	**3h**	89	10:1	95
10	Me	Me	5-OMe	**3i**	92	10:1	97
11	Me	Me	6-Cl	**3j**	91	14:1	94
12	Et	Me	H	**3k**	94	9:1	94
13[e]	Ph	Me	H	**3l**	94	6:1	80
14[e]	furyl	Me	H	**3m**	92	7:1	90

[a] General reaction conditions: 3-substituted oxindole (0.1 mmol, 1 equiv), aldehyde (0.1 mmol, 1 equiv), catalyst (10 mol %), benzoic acid (10 mol %), toluene 0.4 mL (0.25 M); reaction time 24 h; work up employed ice cold 1 M HCl. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude product. [d] Determined by chiral-phase HPLC analysis of major diastereomer. [e] Reaction time 48 h, 20 mol % of catalyst, 20 mol % of benzoic acid, and 0.12 mmol, 1.2 equiv of aldehyde. [f] After single recrystallization.

To further investigate the scope of the reaction, we focused on 3-substituted oxindoles **1b**–**g**. Substituents on the aromatic ring system of the molecule were varied. 5-Methyl, 5-*O*-methyl, and 6-chloro provided products **3h**–**j** in high yields (89–91%) and selectivity (dr's 10:1 to 14:1, ee 94–97%) (Table 2, entries 9–11). We further extended the scope of the reaction from methyl-substituted alkylketone-derived oxindoles to sterically more hindered ethyl and aryl ketones **1e**–**g**. With ethyl-substituted oxindole **1e**, product **3k** was obtained in 9:1 dr and 94% ee (entry 12). Arylketone-derived oxindoles **1f** and **1g** afforded products **3l**–**m** in 80–90% ee, 6:1–7:1 dr, and

(17) For a recent review on diarylprolinol catalysts, see: Lettanzi, A. *Chem. Commun.* **2009**, *12*, 1452.

92−94% yield, although an increased catalyst loading of 20 mol %, 1.2 equiv of aldehyde, and an extended reaction time of 48 h were necessary.

In summary, a highly efficient tandem process was developed for the enantioselective construction of complex spirocyclopentaneoxindoles from simple starting materials in a single step. A wide variety of spirocyclopentaneoxindoles was obtained in high chemical and optical yield from 3-substituted oxindoles and various α,β-unsaturated aldehydes, demonstrating the broad scope of this transformation. The absolute configuration of the products obtained through the iminium−enamine cascade process was determined by X-ray analysis of compound **3f** (see Supporting Information). Commercially available second-generation prolinol ethers promoted the high-yielding one step reaction to provide products with diastereoselectivities up to 17:1 and enantioselectivities up to 99%.

Acknowledgment. Support from the Skaggs Institute for Chemical Biology is gratefully acknowledged. We also thank Drs. A. L. Rheingold and C. E. Moore for X-ray crystallographic analysis (Department of Chemistry and Biochemistry, University of San Diego).

Supporting Information Available. Experimental procedures and compound characterization (^{1}H NMR, ^{13}C NMR, HPLC) including X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.