CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201302131

Asymmetric Organocatalytic Michael/Henry Domino Reactions through Hydrogen-Bond Activation: Kinetic Access to Indane Scaffolds Bearing *cis*-Vicinal Substituents

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Dedicated to Professor Wolfgang Steglich on the occasion of his 80th birthday

The indane scaffold containing *cis*-vicinal substituents is an important chiral motif, which has found significant applications in both bioactive compounds as well as a versatile building block in catalysts for asymmetric synthesis.[1] The first widespread usage of such a building block was first demonstrated by Merck researchers in the development of the HIV protease inhibitor Crixivan (**1**), which still remains one of the leading drugs for AIDS treatment.[2] In addition, many different chiral catalysts incorporate similar *cis*-indane backbones to reach high asymmetric inductions. This includes transition-metal catalysts bearing bis(oxazoline) ligands such as **2**,[3] and asymmetric organocatalysts such as the Rovis *N*-heterocyclic carbene precatalyst **3**,[4] Ricci's chiral thiourea **4**,[5] as well as Seidel's thioamide **5** (Figure 1).[6] Furthermore, oxazaborolidines such as **6** are also an important class of reducing agents for enantioselective reduction reactions.[7]

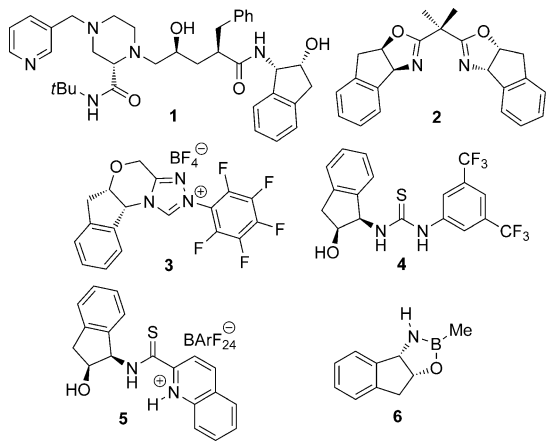
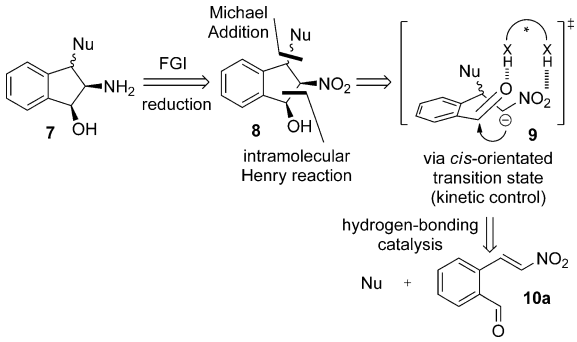


Figure 1. Examples of drugs, ligands and catalysts bearing a chiral indane scaffold with *cis*-vicinal substituents.

While the widespread importance of enantio-enriched *cis*-vicinal indane motifs is undisputed, it is interesting to note that the efficient enantioselective access of such structures is relatively limited. The most commonly utilized method is to employ the asymmetric Mn–(salen)-catalyzed Jacobsen epoxidation on indenes (84–88% *ee*), followed by epoxide opening to provide the *trans*-aminoindanols. The *trans* substrates are then converted to the enantiopure *cis*-aminoindanols after a benzamide crystallization under acidic or Ritter conditions.[8] Alternatively, lengthy enzyme catalysis or the resolution of racemic mixtures are required in order to access this building block.[9] In view of the upsurge of organocatalytic domino reactions in recent years,[10] we postulated that it might be possible to diastereo- and enantioselectively access novel *cis*-vicinal substituted indanes directly through a metal free organocatalytic domino reaction (Scheme 1).



Scheme 1. Retrosynthetic analysis of the organocatalytic *cis*-nitro indanol domino synthesis.

The synthetic challenge of a direct diastereoselective access to *cis*-substituted indanes lies in the thermodynamic unfavorable conformation of two vicinal *cis* substituents. This was very recently demonstrated by Sun et al. in a racemic organo-base catalyzed aza-Michael/aldol domino reaction,[11a] and Csákÿ et al. in a LDA mediated Michael/Michael domino reaction to yield the thermodynamically favored racemic all *trans* indane framework.[11b] In order to impede thermodynamics to yield the kinetic vicinal *cis*-vicinal product **8**, we reasoned that an effective *syn* binding

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302131.

mode by a bi-functional hydrogen-bonding catalyst on both the nucleophile and electrophile in the matched transition state **9** is essential (Scheme 1).[11c,d] Moreover, we also predicted retrosynthetically (Scheme 1) that a simple functional group interconversion from an amino group in **7** to a nitro group in **8** would help to access the *cis*-aminoindanol product **7**, which can be incorporated as a chiral backbone for various purposes.

The other challenge posed in this domino reaction is the presence of two acceptor groups, a nitroolefin and an aldehyde in substrate **10**, which might result in competing side reactions.[12] Hence, it is crucial to select a nucleophile (abbreviated as Nu, Scheme 1) that selectively attacks the nitroolefin and precludes the aldehyde in the first nucleophilic step. While common carbonyl nucleophiles such as aldehyde-derived enolates poses chemoselectivity problems due to a competing aldol reaction, we decided to utilize the Friedel–Crafts type Michael addition of indoles to regioselectively trigger this cascade reaction.[6,13] To the best of our understanding, the currently reported literature examples to access indanols via domino reactions can only be performed resulting in racemic mixtures.[11]

Therefore, we would like to report a kinetically controlled asymmetric organocatalytic Michael addition/intramolecular Henry domino reaction, which allows a facile access to enantio-enriched *cis*-nitroindanol products **12a–m** (see Table 2) that can be easily converted to their useful *cis*-aminoindanol derivatives, such as **7**.[14]

We first conducted a series of experiments to determine the optimal hydrogen-bonding catalyst for the domino reaction (Table 1). We realized that of all catalysts screened, only hydrogen-bonding catalysts **4**, **5** and **13** containing the *cis*-aminoindanol moiety gave the desired kinetic *cis*-cascade product **12a** (Table 1, entries 1, 2, 5). The best result was obtained using Seidel's thioamide catalyst **5** (entry 5) producing almost quantitative yield (98%),[6a] a very good *ee* (87%) and very good d.r (9:1). It is noteworthy to point out that bifunctional catalysts containing basic moieties, such as the catalyst **14** and squareamide **15**, did not yield the desired product **12a** due to product decomposition and a complex mixture was obtained.

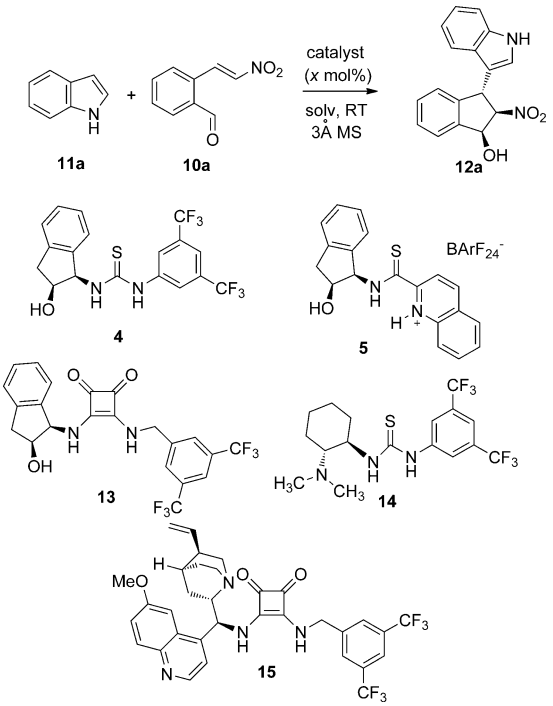
With the best catalyst obtained, we proceeded to screen various solvents for the domino reaction (Table 1, entries 5–10). The best solvent tested was $CHCl_3$ (entry 5). Finally, we lowered the temperature to 0°C (entry 11) and adjusted the catalyst loading, where the optimal condition was obtained at 10 mol% loading of catalyst **5** (Table 1, entry 13) yielding excellent *ee* (93%) and d.r (10:1) and almost quantitative yield (96%).

Subsequently, we proceeded to determine the scope of this useful organocatalytic domino reaction (Table 2).

The cascade reaction turned out to be generally very versatile and a wide spectrum of indoles **11a–j** ranging from electron-withdrawing group to electron donating group containing indoles were found to be extremely well tolerated in this methodology. Moreover, various derivatives of *o*-benzaldehyde nitroolefins containing electron-withdrawing (Cl, **10c**) to electron-donating (OMe, **10b**) substituents were also tolerated to give predominantly the *cis* kinetic products **12a–m**.

In addition, the majority of the yields in the substrate scope were excellent (>90%) with two examples (**12e** and **12m**) achieving almost quantitative yields in the domino reaction, hence substantiating the effectiveness and the efficiency of this methodology. All examples tested also produced excellent enantioselectivity with a very high selectivi-

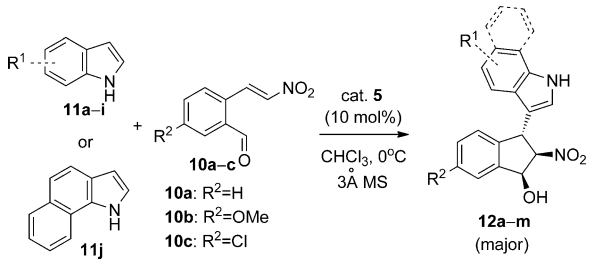
Table 1. Optimization of the reaction conditions.[a,b]



Entry	Cat.	*t* [h]	*x* [mol%]	Solvent	*T* [°C]	Yield [%][c]	d.r[d]	*ee* [%][e]
1	**4**	24	20	$CHCl_3$	23	99	9:1	68
2	**13**	136	10	$CHCl_3$	23	34	9:1	34
3	**14**	16	20	$CHCl_3$	23	–	–	–
4	**15**	7	10	$CHCl_3$	23	–	–	–
5	**5**	14	15	$CHCl_3$	23	98	9:1	87
6	**5**	15	15	1,2-diCl benzene	23	57	8:1	72
7	**5**	15	15	1,3-diCl benzene	23	85	6:1	85
8	**5**	16	15	2,4-diCl benzene	23	85	4:1	86
9	**5**	16	15	1,2,4-triCl toluene	23	83	6:1	82
10	**5**	15	15	toluene	23	80	5:1	81
11	**5**	21	15	$CHCl_3$	0	99	5:1	95
12[f]	**5**	15	5	$CHCl_3$	0	99	9:1	90
13[f]	**5**	17	10	$CHCl_3$	0	96	10:1	93

[a] Reactions were conducted on a 0.2 mmol scale of *o*-benzaldehyde nitroolefin **10a** (1 equiv) and indole **11a** (1.2 equiv). [b] The relative and absolute configuration of **12a** was determined by X-ray crystallography. [c] Yield of isolated **12a** after flash column chromatography. [d] Determined by ^{1}H NMR. [e] Determined by HPLC analysis on a chiral stationary phase. [f] These reactions were conducted on a 0.5 mmol scale of *o*-benzaldehyde nitroolefin **10a**.

Table 2. Scope of the kinetically-controlled Michael/Henry domino reaction.[a,b]



12	R^1	R^2	t [h]	d.r.[c]	*ee* [%][d]	Yield [%][e]
a	H	H	17	10:1	93 (88)	96
b	5-MeO	H	16	9:1	91 (90)	94
c	5-Cl	H	43.5	7:1	92 (92)	61
d	5-Br	H	72	9:1	90 (81)	64
e	5-Me	H	17.5	10:1	90 (91)	>99
f	7-Me	H	17	11:1	97 (95)	95
g	5-F	H	73	9:1	91 (87)	91
h	6-Me	H	18	11:1	91 (89)	98
i	6-Cl	H	63.5	11:1	90 (89)	90
j	–	H	18	9:1	95 (93)	74
k	7-Me	Cl	16.5	17:1	91 (99)	90
l	H	MeO	19.5	11:1	94 (89)	94
m	5-Me	MeO	18	11:1	93 (86)	>99

[a] Reactions were conducted on a 0.5 mmol scale of *o*-benzaldehyde nitroolefin **10a–c** (1 equiv) and indole **11a–j** (1.2 equiv). [b] Relative and absolute configuration of the major diastereomer was determined by analogy to the X-ray crystal structure of derivative **12a**. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase, values in parentheses indicate the *ee* of the minor diastereomer 1-*epi*-**12a–m**. [e] Yields isolated after flash column chromatography.

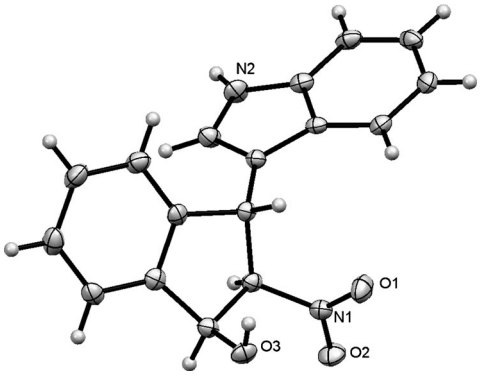
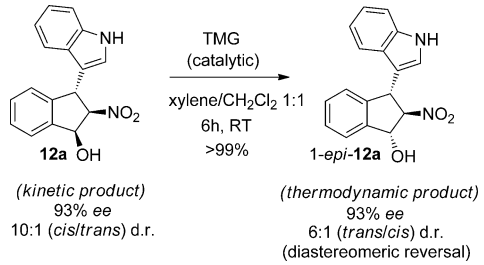


Figure 2. X-ray crystal structure of the major diastereomer **12a**.

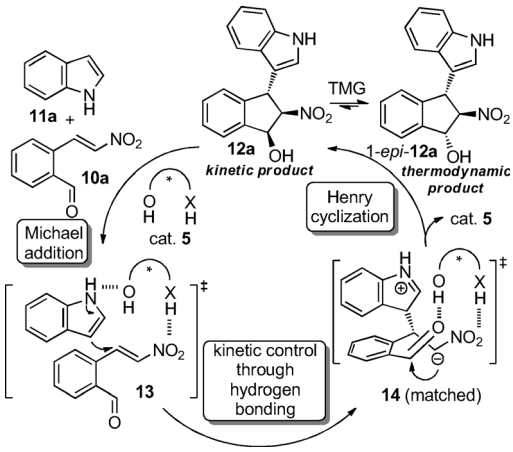
ty for the desired *cis* nitro-indanol diastereomer. The absolute and relative configuration of the major diastereomer was unambiguously determined by X-ray crystallography of derivative **12a** (Figure 2).[15]

To better understand the reaction mechanism, we then proceeded to determine the relative configuration of the minor diastereomer. To achieve this, the major diastereomer **12a** was subjected to a tetramethylguanidine (TMG) catalyzed retro-Henry/Henry epimerization reaction (Scheme 2). Interestingly, we observed that the epimerization proceeded quantitatively and resulted in an enrichment of the minor diastereomer and hence a diastereomeric reversal giving a 6:1 d.r in favor of the thermodynamic all *trans* product 1-*epi*-**12a** without any further epimerization at C2 and C3. The relative configuration of the minor diastereomer 1-*epi*-**12a** is determined by both 1,3-*cis* NOESY contacts and comparing the α and β hydroxyl effects on the ^{13}C NMR shifts (see Supporting Information).[16,17]



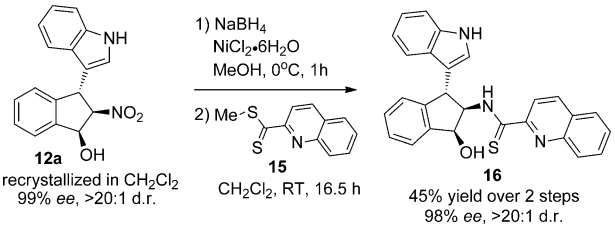
Scheme 2. Thermodynamic base-catalyzed *cis*/*trans* epimerization.

We propose that the domino reaction undergoes a first chemoselective and enantioselective hydrogen-bonding catalyzed Friedel–Crafts type Michael addition through transition state **13** (Scheme 3). After the installation of the first stereocenter, the bifunctional catalyst **5** then forms hydrogen bonds to both the nitro and the aldehyde moiety through a *cis* matched transition state **14**, in preparation for the Henry cyclization step. A final Henry reaction yields the desired *cis* kinetic product **12a**, which can be epimerized to the *trans* thermodyamic product 1-*epi*-**12a** by TMG.



Scheme 3. Proposed mechanism for the domino Michael/Henry reaction.

To demonstrate that the derivatized kinetic cascade product is of synthetic value as a chiral building block, **12a** was first enantio-enriched via a single recrystallization in CH_2Cl_2 to yield **12a** in excellent diastereo- and enantiomeric purity (99% *ee*, >20:1 d.r). **12a** was then further reduced to its corresponding *cis*-aminoindanol, and subsequently attached to form a quinolinyl thioamide precatalyst **16** (Scheme 4).



Scheme 4. Reduction of **12a** to the aminoindanol and further derivatization to the thioamide precatalyst **16**.

In conclusion, we demonstrated that hydrogen-bonding catalysis can be utilized effectively in an asymmetric organocatalytic domino reaction to afford predominantly the *cis*-nitroindanol product by bifunctional kinetic control. The direct asymmetric domino access of the synthetically useful *cis* kinetic product was challenging since all known cases reported gave racemic mixtures, most probably due to chemoselectivity or problems in effecting good kinetic control. In addition, we demonstrated the possibility of attaching the chiral cascade scaffold on a catalyst precursor **16** and this opens up further avenues in utilizing this protocol to access chiral catalysts, ligands or for biological purposes. Further investigations on the utility of the cascade product as a building block in various chiral catalysts and ligands are currently underway in our laboratories.

Experimental Section

A solution of **10a** (0.5 mmol, 1 equiv) in $CHCl_3$ (3 mL) was added to a solution of catalyst **5** (0.05 mmol, 0.1 equiv) and 200 mg activated powdered 3 Å MS in $CHCl_3$ (3 mL). This reaction mixture was cooled to 0 °C. The indole **11a** (0.60 mmol, 1.2 equiv) was then transferred into the cooled reaction mixture. The reaction was monitored by TLC until completion of the domino reaction to form **12a**, which was directly loaded on a flash column for purification.

Keywords: asymmetric synthesis · domino reaction · indole · Michael addition · organocatalysis

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[15] CCDC-933132 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] Only 1,3-*cis* NOESY relationships are useful in determining relative configurations of five membered rings due to ring flexibility, see: a) J. G. Napolitano, J. A. Gávin, C. Gárcia, M. Norte, J. J. Fernández, A. H. Daranas, *Chem. Eur. J.* **2011**, *17*, 6338–6347; the α,β-hydroxyl effects on the ^{13}C NMR shift was consistent with literature reported values of *cis* and *trans* hydroxyl epimers on five-membered rings, see: b) S. Quideau, J. Ralph, *J. Chem. Soc. Perkin. Trans. I* **1993**, *653*–659.

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Received: June 4, 2013
Published online: July 2, 2013

