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Asymmetric domino synthesis of indanes bearing four contiguous stereocentres catalyzed by sub-mol% loadings of a squaramide in minutes†

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Abstract

An efficient diastereo- and enantioselective synthesis of polyfunctionalized indanes bearing four contiguous stereogenic centres in generally very short reaction times and sub-mol% squaramide catalyst loadings has been developed. The novel methodology creates a maximum of two stereocentres per bond formation *via* an organocatalytic Michael–Henry domino reaction.

In recent years, asymmetric organocatalytic domino reactions have developed into a fascinating research area at the forefront of synthetic chemistry leading to diverse and complex molecular structures with very high asymmetric inductions. For the formation of multiple bonds and stereogenic centres in a domino fashion, various organocatalytic activation modes including enamine, iminium, Brønsted acid, Lewis base, hydrogen bonding as well as NHC catalysis are used.¹ However, some common disadvantages the majority of such reactions still encounter are the rather high catalyst loadings often ranging between 5 and 20 mol%,² long reaction times of more than one day, as well as the loss of stereogenic information due to the elimination of water, especially in aldol condensations. With these limitations in mind, we wanted to design a domino reaction fulfilling all of the following four criteria: (1) useful molecular architectures should be assembled with sub-mol% catalyst loadings rivalling transition metal catalysis, (2) maximum stereogenic information should be generated per bond formed (2 stereocentres formed per C–C bond),³ (3) very short reaction times,⁴ and (4) ambient room temperature conditions without temperature control.

Due to our recent interest in accessing synthetically useful chiral indane frameworks via chiral thioamide catalyzed Michael–Henry domino reactions (Scheme 1, eqn (1)),^{5,6} we envisioned that *N*-Boc-protected oxindoles containing an sp³ nucleophilic carbon (Scheme 1, eqn (2)) could ensure that the nucleophilic carbon forms a stereogenic center in the domino sequence to achieve a maximum conservation of stereogenic information per bond formed,⁷ in contrast with the previously published report resulting in only a calculated 1.5 stereogenic centers per bond formed in the domino reaction.⁵

†Electronic supplementary information (ESI) available: Experimental procedures, characterization data of all products, ¹H and ¹³C NMR spectra, and HPLC chromatograms. See DOI: 10.1039/c3cc46033a

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We would now like to report on an asymmetric Michael–Henry domino reaction that proceeds in a very short reaction time catalyzed by sub-mol% amounts of a squaramide, which allows a facile access to *cis*-nitroindanols bearing four contiguous stereogenic centres with excellent diastereo- and enantioselectivities.⁸ Our initial intention was to test chiral Brønsted base catalysis by employing TMS-protected dialkylprolinol **4**⁹ used previously by our group,^{10–12} To our delight, **4** (Table 1, entry 1) catalyzed the Michael–Henry domino reaction of oxindole **1a** with nitrovinyl benzaldehyde **2a** to form the indane cascade product **3a** at room temperature in moderate enantioselectivities (44%). A lower temperature of –25 °C gave only a modest increase in ee to 59% with a virtually quantitative yield (Table 1, entry 2). Encouraged by these results, we screened the commonly utilized TMS-protected diphenylprolinol derived catalysts **5** and **6**. However, this change from alkyl to aryl substitution on the praline-derived catalyst resulted in a decrease in enantioselectivities (Table 1, entries 3 and 4).

Subsequently, the quinine-derived primary amine **7** was tested in this domino reaction (Table 1, entry 5). While the enantioselectivity in this case showed a marked increase in ee to 80%, yields dropped to 32% and the d.r. also decreased to 8:1. We then screened bi-functional hydrogen bonding catalysts. Upon utilizing the Takemoto thiourea catalyst **8**, excellent enantioselectivities were achieved (Table 1, entry 6), albeit with only moderate yields and lower d.r. (66%, 7:1 d.r.).

When the bi-functional squaramide catalyst **9** was utilized in the domino reaction, we observed a significant increase in the reaction rate (2.5 h), and the cascade product was obtained with excellent yields, d.r. and enantioselectivities (Table 1, entry 7). When the quinine derived-squaramide catalyst **10** was tested, we noticed a slight increase in ee (95%) with an almost quantitative yield and d.r. within 1.5 h. Remarkably, the catalyst loading of **10** could be effectively decreased to sub-mol% quantities (Table 1, entries 9–11) with the optimal catalyst loading obtained at 0.5 mol%. Finally, the stoichiometric proportions of substrates **1** and **2** were optimized to provide excellent yields, ee and d.r. values of the cascade product **3a** within 45 minutes (Table 1, entry 12).

With the optimized conditions in hand, we then proceeded to screen the substrate scope of this rapid and highly efficient Michael–Henry domino reaction (Table 2).

We figured out that generally this protocol is highly efficient and tolerant towards a wide series of functional groups. These include compounds containing electron donating (Table 2, **3c**, **g** and **k**) and electron withdrawing groups (Table 2, **3b**, **d**, **f**, and **h**, **j** and **l**). Moreover, the enantioselectivities were generally excellent. The diastereomeric ratios of this Michael–Henry domino reaction were also excellent (20:1) for most of the examples tested (Table 2, **3a–l**). For **3j** a slight increase in catalyst loading to 1 mol% was required in order to obtain excellent ee, however, we also noticed that this reaction was completed in only 20 minutes at room temperature.

One limitation of this methodology is that R² requires a phenyl or a phenyl derivative substituent. When a methyl substituent (Table 2, **3m**) or a hydrogen substituent (Table 2, **3n**) was tested, yields and enantioselectivity became inferior. Decomposition was observed in

the reaction and workup when a thiophene substituent was used in R^2 (Table 2, **3o**) and the cascade product could not be isolated. One explanation is that the presence of a phenyl group on R^2 is crucial in this methodology to stabilize the carbanion formed at C3 of the oxindole.

The relative configuration of the cascade products **3a–n** was determined by analogy to long range NOESY contacts of derivatives **3a** and **3b**. The absolute configuration was determined by comparing the relative toxicity of this domino reaction using catalyst **10** with literature known Michael additions of *N*-Boc-oxindoles using catalyst **4** (Table 1, comparing entries 2 and 12, for a detailed mechanism, see ESI[†]).¹⁰

We also tested a gram scale synthesis of the cascade product **3g**. Interestingly, we noticed that the gram scale synthesis proceeded much faster in 15 minutes with reproducible results comparable to the 0.5 mmol scale (Table 2, **3g**) with excellent yield and very good ee (Scheme 2).

The gram scale reaction however resulted in a slight decrease of the d.r. to 17:1. This lower d.r. was overcome by triturating **3g** in diethylether overnight thus raising the diastereoselectivity to >20:1 d.r. Furthermore, a Boc-deprotection was carried out on **3g** by stirring it with TFA. The facile deprotection resulted in almost quantitative yield of the deprotected derivative **11** (96%).

In conclusion, an efficient asymmetric organocatalytic Michael–Henry domino reaction has been developed that generates polyfunctionalized indanes bearing four contiguous stereogenic centers with sub-mol% catalyst loadings. This new scalable protocol is based on the hydrogen bonding activation of the squaramide catalyst and creates a maximum of two stereogenic centres per bond formation within minutes. Further investigations of the utility of the cascade products are currently underway in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Notes and references

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Scheme 1.

Domino efficiency comparison of current with previously reported work.

Scheme 2.

Gram scale synthesis of the cascade product **3g** and further transformation.

Table 1

Optimisation of the reaction conditions^{a,b}

Entry	Cat.	<i>t</i>	Cat. loading (mol%)	Yield ^c (%)	d.r. ^d	ee ^e (%)
1	4	18 h	10	77	>20:1	44
2 ^f	4	18 h	10	99	>20:1	59
3	5	23 h	10	97	>20:1	-17
4	6	2 h	10	78	>20:1	27
5	7	16.5 h	10	32	8:1	80
6	8	16.5 h	20	66	7:1	-91
7	9	2.5 h	10	98	>20:1	-93
8	10	1.5 h	10	99	>20:1	95
9	10	15 min	5	96	20:1	91
10 ^g	10	40 min	1	68	>20:1	90
11 ^g	10	45 min	0.5	81	>20:1	91
12 ^h	10	45 min	0.5	93	>20:1	93

^a Conducted on a 0.1 mmol scale of **1a** (1 equiv.) and 0.12 mmol scale of **2a** (1.2 equiv.).^b The relative and absolute configurations of **3a** were assigned by analogy to 2D NOESY of **3a** and **b** and comparing with literature data.¹⁰^c Yields of isolated **3a** after flash column chromatography.^d Determined by ¹H NMR.^e Determined by HPLC analysis on a chiral stationary phase.^f This reaction was conducted at -25 °C.^g Reactions were conducted on a 0.5 mmol scale of **1a** (1 equiv.) and 0.6 mmol scale of **2a** (1.2 equiv.).^h Reaction was conducted on a 0.55 mmol scale of **1a** (1.1 equiv.) and 0.5 mmol scale of **2a** (1 equiv.).

Table 2

Substrate scope of the Michael–Henry domino reaction^{a,b}

3	R ¹	R ²	R ³	ee ^c (%)	Yield ^d (%)
a	Me	Ph	H	93	93
b	Me	Ph	Cl	90	89
c	Me	Ph	MeO	90	95
d	Me	Ph	F	90	83
e	H	Ph	H	90	86
f	H	Ph	Cl	90	92
g	H	Ph	MeO	90	92
h	H	Ph	F	89	87
i	Me	<i>p</i> -Ph-Ph	H	98	87
j ^e	Me	<i>p</i> -Ph-Ph	Cl	99	83
k	Me	<i>p</i> -Ph-Ph	MeO	89	92
l	Me	<i>p</i> -Ph-Ph	F	91	90
m ^f	H	Me	Cl	39	39
n ^g	H	H	Cl	73	44
o	H	2-Thiophenyl	Cl	—	—

^aThe reaction was conducted on a 0.55 mmol scale of **1a-n** (1.1 equiv.) and 0.5 mmol scale of **2a-d** (1 equiv.).^bThe relative and absolute configurations of **3a-n** were assigned by analogy to 2D NOESY of **3a** and **b** and comparison with literature data.¹⁰^cDetermined by HPLC analysis on a chiral stationary phase.^dYields of isolated **3a-n** after flash column chromatography.^eConducted with 1 mol% of catalyst **10** for 20 min.^f3 Equiv. oxindole **1m** was used; reaction time was extended to 220 min.^g3 Equiv. oxindole **1n** was used; d.r was 12:1 in this case.