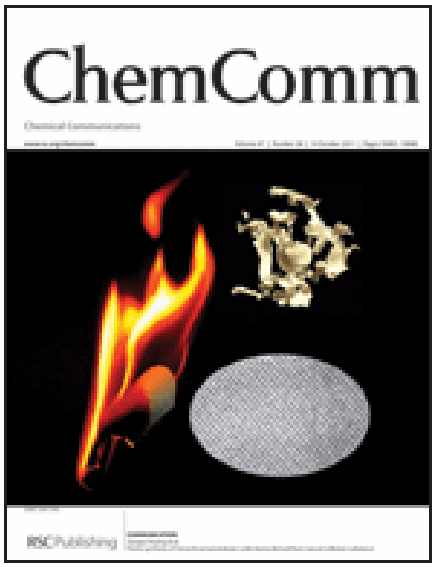

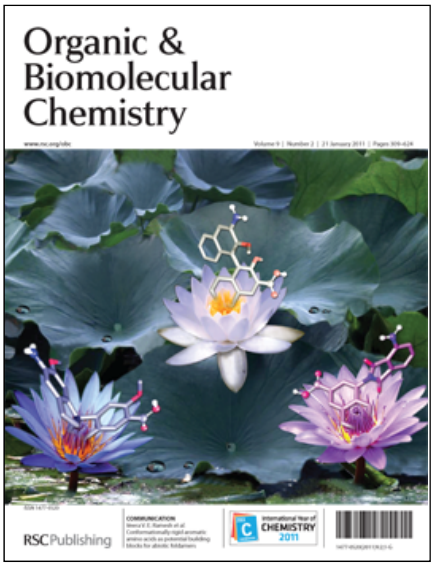

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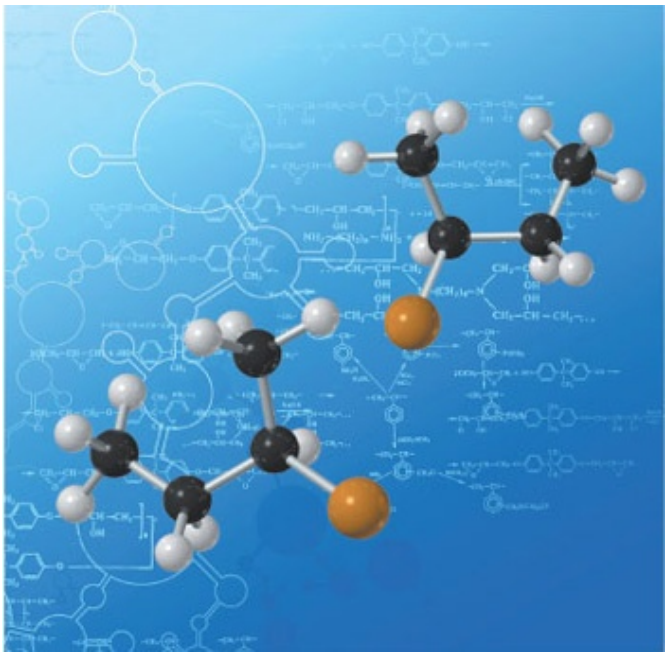

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COMMUNICATION

Discovery of 2-aminobuta-1,3-enynes in asymmetric organocascade catalysis: construction of drug-like spirocyclic cyclohexanes having five to six contiguous stereocenters†‡

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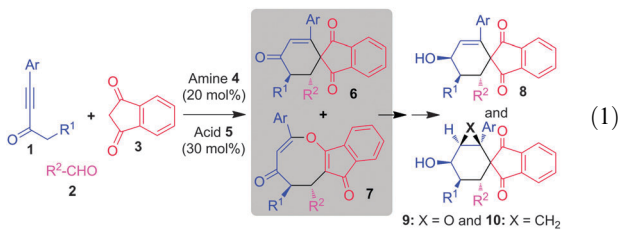
We present herein for the first time the asymmetric synthesis of drug-like spiranes through reflexive-Michael reaction by using 2-aminobuta-1,3-enyne catalysis under mild conditions.

Despite rapid progress in asymmetric organocascade catalysis,[1] practical and efficient asymmetric cascade approaches remain in high demand. An ideal asymmetric organocascade catalysis reaction would be atom-economical, of high substrate scope, rapid, and performed under mild conditions to yield quantitative and enantiomerically pure products with simple catalysts and substrates.[2] Since the reflexive-Michael (*r*-M) or Diels–Alder (D–A) reaction is arguably the most powerful organic transformation available for the synthesis of complex cyclohexanes,[3] development of new and highly efficient organocatalytic cascade approaches to this reaction is significant. Organocatalytic asymmetric D–A reactions have been approached using MacMillan iminium catalysis,[4] Barbas dienamine catalysis,[5] Serebryakov dienamine catalysis,[6] Tan–Deng acid–base catalysis,[7] and Schreiner–Rawal hydrogen-bonding catalysis.[8] For the first time, here we describe an unusually efficient organocascade asymmetric *r*-M reaction through *in situ* formation of *2-aminobuta-1,3-enynes* and *2-arylidene-indan-1,3-diones* from simple substrates and catalysts by using sequential iminium–enamine–iminium activation.



(1)

Spirocyclic cyclohexane scaffolds are present in many natural and unnatural compounds that exhibit important biological and physical activities (eqn S1, see ESI‡).[9] Recently, biphenyl-based spirocyclic ketones have shown well-defined activity upon apoptosis and differentiation, making them potential leads for the development of new anticancer agents.[9b] However, there is no suitable asymmetric method to prepare these kinds of compounds in enantiomerically pure form with more functional diversity.

As our group is working on the development of asymmetric cascade synthesis of drug-like compounds,[10] herein we propose that medicinally important spirocyclic skeletons **6–10** with multiple stereocenters could be constructed through newly designed asymmetric *r*-M reactions between ynones **1**, aldehydes **2** and indane-1,3-dione **3** with suitable organocatalysts **4** and co-catalysts **5** followed by a few high-yielding reduction, oxidation and Simmons–Smith transformations (eqn (1)).

We were surprised to find that the designed cascade reaction of ynone **1a**, benzaldehyde **2a** and indane-1,3-dione **3** with a catalytic amount of L-proline **4a** in EtOH at 25 °C for 72 h furnished the homocyclic *r*-M product **6aa** in only <5% yield (Table 1, entry 1). Same reaction under the catalysis of L-diamine/benzoic acid **4b**/**5a** in toluene at 25 °C for 26 h furnished the *r*-M product **6aa** in 18% yield with 28% ee, which was accompanied by heterocyclic *r*-M product **7aa** in 65% yield with 44% ee (entry 2). Same cascade reaction under the **4b**/**5a** catalysis in toluene at reduced temperature (−5 °C) for 48 h furnished the **7aa** in 60% yield with 64% ee, which was accompanied by the minor product **6aa** in 10% yield with 18% ee (entry 3). One quick crystallization of the **(+)-7aa** in *i*-PrOH/Hex (2 : 1) at 25 °C, enriched the ee up to 91% (entry 3). In the *r*-M reaction of **1a**, **2a** and **3** catalyzed by **4**/**5**, we found that the solvent, temperature and nature of the amine/acid catalyst had a significant effect on the outcome of chemoselectivity, yields and ee's (Table 1).

Based on the various applications of spirocyclic ketones **6**, we showed interest in improving the competition towards the homocyclization over the heterocyclization of the designed cascade reaction. We tested the less basic D-DPPOTMS **4c** and topologically interesting primary amines **4d** and **4e** as catalysts to improve the formation of *r*-M product **6aa**. Reaction of **1a**, **2a** and **3** upon the catalysis of **4c**/**5a** in toluene at 25 °C for 48 h furnished the **6aa** in 60% yield with 37% ee, and **7aa** in only 5% yield (Table 1, entry 4). Among the various conditions screened, surprisingly **4d**/**5b** in toluene at 25 °C for 24 h proved

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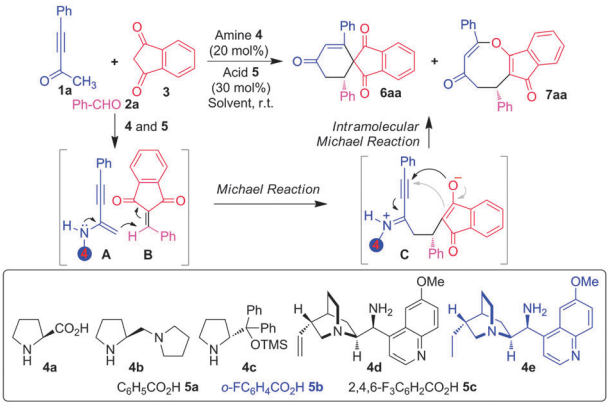
‡ Electronic supplementary information (ESI) available: Experimental procedures and analytical data for all new compounds. CCDC 848633 **((+)-6ee)** and 848634 **((+)-6be)**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17219d

Table 1 Reaction optimization[a]



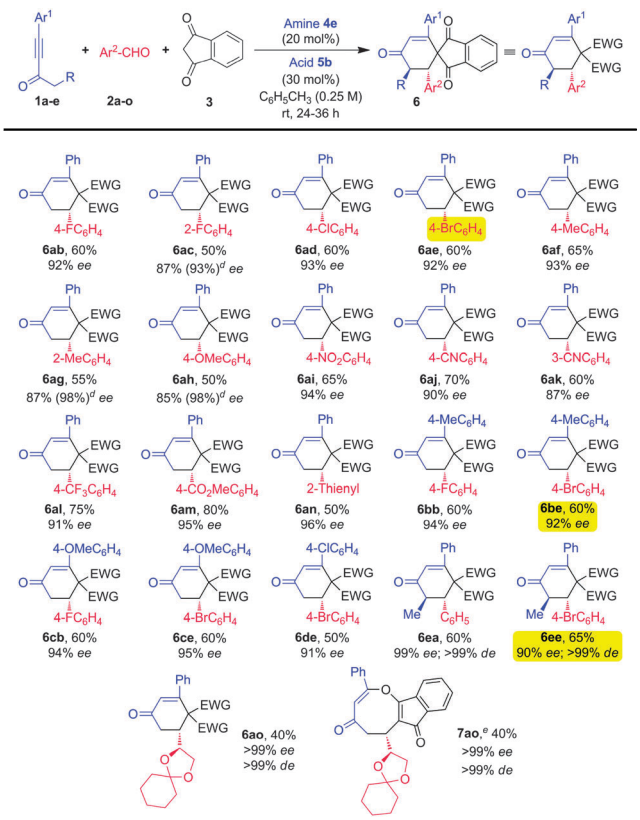
Entry	Catalyst **4**/**5** (20/30 mol%)	Solvent (0.25 M)	Time/h	Product yields[b] (%) **6aa**	**7aa**	ee[c] (%) **6aa**	ee[c] (%) **7aa**
1	**4a**	EtOH	72	<5	—	—	—
2	**4b**/**5a**	$C_6H_5CH_3$	26	18	65	28	−44
3[d]	**4b**/**5a**	**$C_6H_5CH_3$**	**48**	**10**	**60**	**18**	**−64 (91)**[e]
4	**4c**/**5a**	$C_6H_5CH_3$	48	60	5	37	—
5	**4d**/**5a**	Brine	36	75	10	80	57
6	**4d**/**5a**	Et_2O	36	50	5	89	16
7	**4d**/**5a**	$C_6H_5CH_3$	36	70	5	89	31
8	**4d**/**5b**	$C_6H_5CH_3$	24	70	7	92	43
9	**4e**/**5b**	**$C_6H_5CH_3$**	**24**	**70**	**10**	**95 (>99)**[e]	**55**
10	**4e**/**5c**	$C_6H_5CH_3$	24	60	6	94	46
11[d]	**4e**/**5b**	**$C_6H_5CH_3$**	**72**	**25**	—	**97**	—

[a] Reactions were carried out in solvent (0.25 M) with 2 equiv. of **1a** relative to **2a** (0.2 mmol) and **3** (0.2 mmol) in the presence of 20/30 mol% of catalyst **4**/**5**. [b] Yield refers to the column-purified product. [c] ee determined by CSP HPLC analysis. [d] Reaction performed at −5 °C. [e] ee values in parentheses obtained from one quick crystallization of **6**/**7** in *i*PrOH/hex at 25 °C.

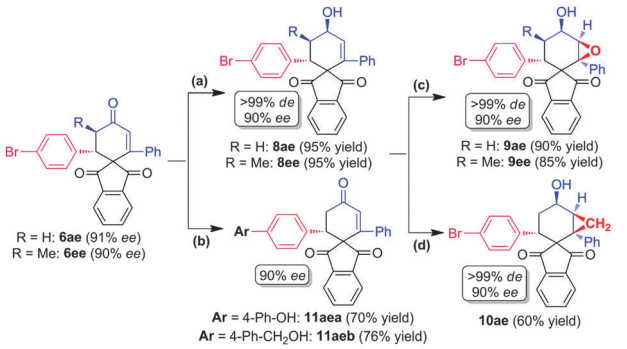
to be the good conditions for homocyclization with respect to yield and ee, providing **6aa** in 70% yield with 92% ee and **7aa** in only 7% yield with 43% ee (entry 8). Further optimization of this reaction under the **4e**/**5b** catalysis furnished the **6aa** in 70% yield with 95% ee, and **7aa** in only 10% yield with 55% ee (entry 9). There is not much improvement in the yield and ee of the reaction beyond these conditions as found in **4e**/**5c**, and at the low temperature **4e**/**5b**-catalyzed *r*-M reactions (entries 10 and 11). One quick crystallization of **(+)-6aa** (95% ee) in *i*-PrOH/Hex (2 : 1) at 25 °C enriched the ee up to >99% with 80% crystallization yield (entry 9). In the final optimization, cascade *r*-M reaction of **1a**, **2a** and **3** through **4e**/**5b** catalysis furnished the chiral spirotrione **(+)-6aa** in 70% yield with >99% ee (Table 1, entry 9). Pure *r*-M products **6aa** and **7aa** were treated under both optimized reaction conditions to test the interconversion, because of their reactive enone group. Interestingly, **7aa** was able to transform into **6aa** in 60–80% conv. with 20–60% yields under **4b**/**5a** or **4e**/ **5b** catalysis at 25 °C for 24/8 h, respectively. But this conversion rate is very slow when ynone **1a** is around, because catalyst amine will be more reactive towards ynone **1a** instead of **7aa**. Surprisingly, there is no reaction of **6aa** with **4b**/**5a** or **4e**/**5b** catalysis at 25 °C for 24 h (Scheme S1, see ESI‡).

We further explored the scope of the primary amine/acid-catalyzed *r*-M reaction by developing diversity-oriented synthesis of optically pure spirocyclic cyclohexenones **6ab–ao** and **6bb–ee** through cascade reaction of ynones **1a–e**, aldehydes **2a–o** and indan-1,3-dione **3** (Table 2).[11] The chiral spiranes **6** were obtained in good to excellent yields and excellent ee/de's with a variety of aldehydes containing neutral, electron-donating, electron-withdrawing, halogenated, hetero-atom substituted and aliphatic Ar(R)-CHO **2a–2o** and ynones containing neutral, electron-donating, electron-withdrawing, and halogenated **1a–1e** from the asymmetric *r*-M reaction (Table 2). Surprisingly, formation of the *r*-M products **7** from above reactions was observed only in 0–5%. Herein, a variety of ynones **1a–e** are used as source for the *in situ* generation of *2-aminobuta-1,3-enynes* in a cascade *r*-M reaction to furnish the spirotriones **6ab–6ao** and **6bb–6ee** with 85 to >99% ee and >99% de in good to excellent yields (Table 2).[12] The cascade reaction of ynone **1a**, chiral aldehyde **2o** and **3** under the catalysis of **4b**/**5a** furnished only the heterocyclic *r*-M product **7ao** in 40% yield with >99% ee/de (Table 2, entry 22). The structure and absolute stereochemistry of the cascade *r*-M products **6** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis of **(+)-6be** and **(+)-6ee** as shown in Fig. S1 and S2 (see ESI‡).

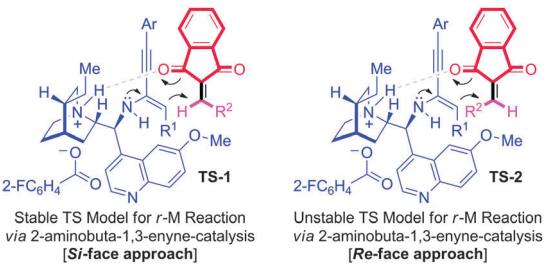
Table 2 Scope of the new reaction[a,b,c]



[a] Reactions were carried out in toluene (0.25 M) with 2 equiv. of **1** relative to **2** (0.2 mmol) and **3** (0.2 mmol) in the presence of 20/30 mol% of catalyst **4e**/**5b**. [b] Yield refers to the column-purified product. [c] ee and de determined by CSP HPLC analysis. [d] ee values in parentheses obtained from quick crystallization of **6** in *i*PrOH/hex at 25 °C. [e] Reaction performed under the catalysis of **4b**/**5a** (20/30 mol%).



Scheme 1 Synthesis of drug-like spiranes for anticancer studies. *Reaction conditions:* (a) $NaBH_4$ (1.5 equiv.), dry CH_3OH (0.25 M), 0–25 °C, 0.5 h; (b) Ar-$B(OH)_2$ (2.0 equiv.), $Pd(PPh_3)_4$ (0.055 equiv.), $C_6H_5CH_3$ (2 mL), sodium succinate (4.2 equiv.), $C_6H_5CH_3$: H_2O (1.14 : 1; 1.5 mL), EtOH (1.4 mL), 90 °C, 8 h; (c) *m*CPBA (1.2 equiv.), CH_2Cl_2 (0.2 M), 0–25 °C, 2 h; (d) CH_2I_2 (5.0 equiv.), Et_2Zn (5.0 equiv.), CH_2Cl_2 (0.065 M), −10 °C to 25 °C, 4 h.

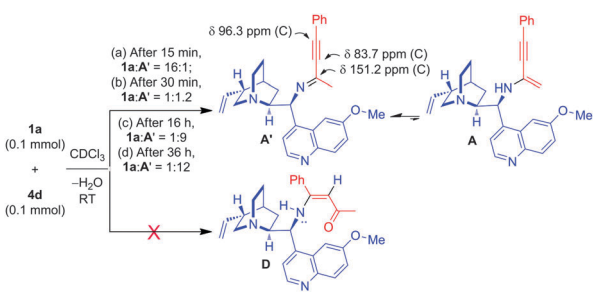


Stable TS Model for *r*-M Reaction *via* 2-aminobuta-1,3-enyne-catalysis [*Si*-face approach]

Unstable TS Model for *r*-M Reaction *via* 2-aminobuta-1,3-enyne-catalysis [*Re*-face approach]

(2)

Although further studies are needed to firmly elucidate the mechanism of *r*-M reactions through **4e**/**5b** catalysis, the reaction proceeds in a stepwise manner between *in situ* generated *2-aminobuta-1,3-enynes* **A** and *2-arylidene-indan-1,3-diones* **B** (eqn (2)). Based on the crystal structure studies, we can rationalize the observed high stereoselectivity through an allowed transition state where the *si*-face of **B** approaches the *re*-face of enyne **A** due to the strong hydrogen-bonding/electrostatic/CH–π interactions and less steric hindrance as shown in **TS-1**. Formation of the minor enantiomer may be explained by model **TS-2**, in which there is strong steric hindrance between the alkyl portion of the catalyst and the aryl group of **B** (eqn (2)). *In situ* formation of the proposed reactive species *2-aminobuta-1,3-enyne* **A** and *imine* **A′** from **1a** and **4d** in $CDCl_3$ at 25 °C was established through the controlled NMR experiment (eqn (3)). In this NMR experiment, we have observed only the formation of 1,2-addition products **A**/**A′** and we didn't see the 1,4-addition intermediate **D**.



(3)

With the medicinal applications in mind, we explored the utilization of spiranes **6** bearing aryl bromide in the high-yielding synthesis of functionalized chiral spiranes **8–11** having five to six contiguous stereogenic centers *via* simple reduction, epoxidation, Simmons–Smith cyclopropanation and Suzuki coupling transformations (Scheme 1). Discussions on reaction details, yields and selectivities are summarized in ESI‡-1, and some of the compounds **(+)-11aea** and **(+)-11aeb** obtained from *r*-M and Suzuki coupling sequence are drug-like molecules for the treatment of cancer cells, which emphasizes the value of this *r*-M and Suzuki coupling approach to the pharmaceutical industry.[9]

In summary, for the first time we have developed the chiral primary amine/acid **4e**/**5b**-catalyzed asymmetric *r*-M reaction of ynones with aldehydes and indane-1,3-dione to furnish the spiranes under ambient conditions via *2-aminobuta-1,3-enyne*-catalysis.

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Notes and references

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