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Asymmetric Quadruple Aminocatalytic Domino Reactions to Fused Carbocycles Incorporating a Spirooxindole Motif

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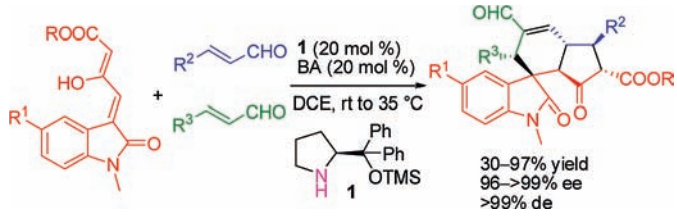
ABSTRACT



The efficient assembly of hydroindane derivatives incorporating a spirooxindole motif was realized via a new three-component domino reaction of (*E*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoates and two molecules of α,β-unsaturated aldehydes under quadruple iminium−enamine−iminium−enamine catalysis. The complex products bearing six contiguous stereogenic centers were obtained in excellent stereoselectivities (96−>99% ee, >99% de).

The economic and effective concerns in organic synthesis provoke increasing attention because of the current emphasis on the development of green and sustainable chemistry.[1] The catalytic domino or cascade reactions would satisfy most of the criteria for such purposes, and consequently, many efforts have been devoted to this area.[2] Over the past years, fruitful results on asymmetric domino reactions have been presented by the catalysis of environmentally benign small organic molecules.[3] Among them, the elegant combination of enamine and iminium activation modes for carbonyl compounds by amine catalysts provides a very attractive strategy for the design of asymmetric domino sequences, from which a diversity of multifunctional products, including variously structured carbocycles and heterocycles, have been generated.[4] Currently, the expansions to exemplify the power of domino aminocatalysis are actively continuing.[5] Nevertheless, the examples involving *multiple* catalytic modes, which can allow rapid constructions of high levels of molecular complexity and stereoselectivity, are still limited.[6]

Recently, we have developed a highly stereoselective domino Michael−Wittig reaction of (3-carboxy-2-oxopropylidene)triphenylphosphoranes and α,β-unsaturated alde-

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(1) For a tutorial review, see: Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(2) For reviews, see: (a) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (b) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (c) Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092.

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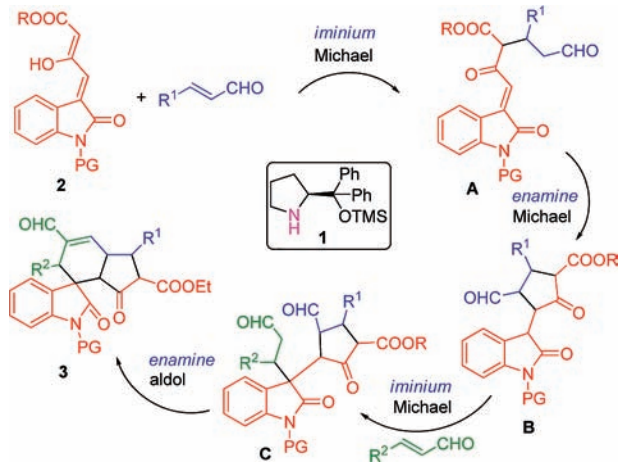
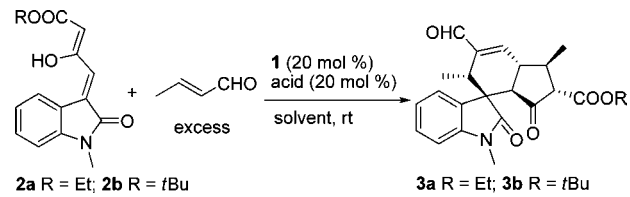
hydes to access chiral cyclohex-2-en-1-ones by using iminium catalysis as the key stereocontrolling step.[7] On the other hand, we and Melchiorre et al. independently reported an efficient three-component cascade reaction of aliphatic aldehydes, 3-olefinic oxindoles, and α,β-unsaturated aldehydes to deliver spirooxindoles incorporating a six-membered cyclic moiety by triple enamine−iminium−enamine catalysis.[8,9] Based on these achievements, we were intrigued in the design of a novel type of multifunctional synthons **2**, 3-oxo-4-(2-oxoindolin-3-ylidene)butanoates, which possess multiple reactive sites and might successively perform as nucleophiles and electrophiles in a proper cascade process. We envisaged that a three-component domino reaction of **2** and two molucules of α,β-unsaturated aldehydes might be feasible by a quadruple iminium−enamine−iminium−enamine catalysis of chiral secondary amine, such as readily available α,α-diphenylprolinol *O*-TMS ether **1**,[10] as oultined in Scheme 1. Thus, densely substituted hydroindane frameworks **3** incorporating an interesting spirooxindole motif would be constructed with high synthetic economy and effectiveness.[11]

Scheme 1. Proposed Quadruple Aminocatalytic Domino Sequences to Fused Carbocycles



Inspired by these considerations, we initially investigated the domino reaction of multifunctional substrate **2a** and excess crotonaldehyde (4 equiv) by the catalysis of **1a** (20 mol %) and benzoic acid (BA) in toluene at ambient temperature.[12] To our gratification, **2a** was consumed smoothly, and the desired fused carbocycle **3a**, bearing six contiguous stereocenters, was isolated in 28% yield with excellent stereoselectivity (Table 1, entry 1, >99% ee, >99% de), while a few unidentified byproducts were also observed. Subsequently, some solvents were screened (entries 2−5), and a slightly better yield was obtained in 1,2-dichloroethane (DCE, entry 5). Similar data were afforded when benzoic

Table 1. Screening Studies of Domino Reaction of Multifunctional **2** and Excess Crotonaldehyde[a]



entry	solvent	enal (equiv)	additive	time (h)	yield[b] (%)	ee[c] (%)
1	toluene	4	BA	4	28	>99
2	$PhCF_3$	4	BA	5	34	>99
3	THF	4	BA	24	<10	
4	DCM	4	BA	24	<10	
5	DCE	4	BA	14	43	>99
6	DCE	4	OFBA	14	34	>99
7	DCE	4	AcOH	22	44	>99
8	DCE	2.1 + 1	BA	24	55	>99
9[d]	DCE	2.1 + 1	BA	30	60	>99
10[d,e]	DCE	2.1 + 1	BA	70	66	>99
11[d,e,f]	DCE	2.1 + 1	BA	36	66	>99

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a**, excess crotonaldehyde, 20 mol % of **1**, and acid in 1.0 mL of solvent at rt. [b] Yield of isolated **3**. [c] Based on chiral HPLC analysis; >99% de. [d] In 2.0 mL of solvent. [e] **2b** was used; yield for **3b**. [f] At 35 °C.

(5) For selected recent examples, see: (a) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (b) Albrecht, L.; Richter, B.; Vila, C.; Krawczyk, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2009**, *15*, 3093. (c) McGarraugh, P. G.; Brenner, S. E. *Org. Lett.* **2009**, *11*, 5654. (d) Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5701. (e) Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196. (f) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892. (g) Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627. (h) Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6844. (i) Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481. (j) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem.—Eur. J.* **2010**, *16*, 440. (k) Zhang, W.; Franzén, J. *Adv. Synth. Catal.* **2010**, *352*, 499.

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(8) (a) Jiang, K.; Jia, Z.-J.; Chen, S.; Wu, L.; Chen, Y.-C. *Chem.—Eur. J.* **2010**, *16*, 2852. (b) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200.

(9) For other catalytic asymmetric reactions to construct chiral spirocyclic oxindoles, see: (a) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (b) Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5820. (c) Shintani, R.; Hayashi, S.-y.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754. (d) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (e) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008.

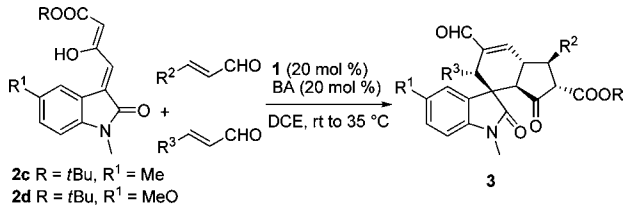
(10) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243.

(11) For selected examples containing polyhydroindane structures, see: (a) Rancitshomasm, A.; Zainne, I.; Untz-Dubini, R. *Can. J. Chem.* **1980**, *58*, 1810. (b) Srikrishna, A.; Vijaykumar, D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1265. (c) Tori, M.; Makino, C.; Hisazumi, K.; Sono, M.; Nakashima, K. *Tetrahedron: Asymmetry* **2001**, *12*, 301. (d) Hess, B. A., Jr. *Org. Lett.* **2003**, *5*, 165. (e) Sha, C.-K.; Liao, H,-W.; Cheng, P.-C.; Yen, S.-C. *J. Org. Chem.* **2003**, *68*, 8704. (f) Maity, S.; Ghosh, S. *Tetrahedron* **2009**, *65*, 9202. (g) Rahman, M. M.; Garvey, M.; Piddock, L. J. V.; Gibbons, S. *Phytother. Res.* **2008**, *22*, 1356.

acid was replaced by *o*-fluorobenzoic acid (OFBA, entry 6) or acetic acid (entry 7). We found that the yield could be improved by adding crotonaldehyde in two potions and diluting the reaction solution (entries 8 and 9). Moreover, cleaner reaction was attained when **2b** with a *tert*-butyl ester group was applied (entry 10), even at higher reaction temperature (entry 11).

Consequently, the substrate scope and limitations were explored under the optimized reaction conditions. The results were summarized in Table 2. For multifunctional substrate

Table 2. Substrate Scope and Limitations[a]



entry	**2**	R^2	R^3	time (h)	yield[b] (%)	ee[c] (%)
1	**2b**	Me	Me	36	**3b**, 66	>99
2	**2b**	Ph	Ph	24	**3c**, 73	>99
3	**2b**	*p*-FPh	*p*-FPh	24	**3d**, 91	>99
4	**2b**	*m*-ClPh	*m*-ClPh	21	**3e**, 81	>99
5	**2b**	*o*-BrPh	*o*-BrPh	20	**3f**, 84	>99
6	**2b**	*p*-MeOPh	*p*-MeOPh	19	**3g**, 78	>99
7	**2b**	2-thienyl	2-thienyl	40	**3h**, 93	>99[d]
8	**2b**	1-propenyl	1-propenyl	41	**3i**, 30	>99
9	**2c**	Me	Me	48	**3j**, 69	>99
10	**2d**	Ph	Ph	11	**3k**, 97	>99
11[e]	**2a**	Ph	Me	31	**3l**, 40	>99
12[e]	**2a**	*o*-ClPh	Me	68	**3m**, 47	96
13[e]	**2a**	*p*-MeOPh	Me	70	**3n**, 45	>99
14[e]	**2a**	2-thienyl	Me	68	**3o**, 32	>99
15[e]	**2a**	Ph	1-propenyl	72	**3p**, 30	>99

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2**, 2.2−3.1 mmol of enal, 20 mol % of **1**, and benzoic acid in 2.0 mL DCE at 35 °C. See the Supporting Information for details. [b] Yield of isolated **3**. [c] Based on chiral HPLC analysis; >99% de. [d] The absolute configuration of **3h** was determined by X-ray crystallographic analysis (Figure 1). The other products were assigned by analogy. [e] After the consumption of **2a** with a β-aryl-substituted enal (1.1 equiv, at rt, for 2 h), another enal (1.5 equiv) was added at 35 °C.

2b, a number of α,β-unsaturated aldehydes with a β-aryl group, either bearing electron-withdrawing or electron-donating substitutions, could be efficiently utilized. The expected spirocyclic compounds **3c**−**g** were obtained in good to high yields and excellent stereoselectivities (entries 2−6). The results were also remarkable for an enal with a heteroaryl substitution (entry 7), and the structure of product **3h** was unambiguously determined by X-ray crystallographic analysis (Figure 1). Interestingly, the regioselective Michael addition could be realized when 2,4-hexadienal was em-

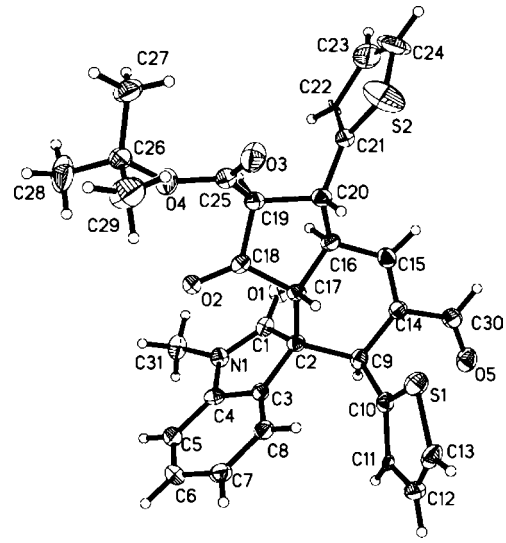
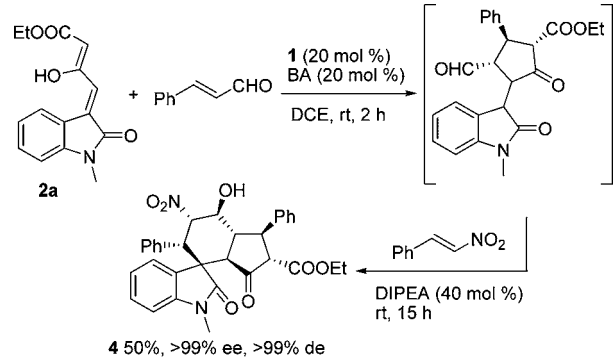


Figure 1. X-ray structure of enantiopure **3h**.

ployed. Product **3i** possessing more functionalities was isolated in outstanding stereoselectivity, albeit in low yield (entry 8). The introduction of electron-donating substituent to oxindole moiety provided slightly better outcomes in the domino reaction (entries 9 and 10).[13] On the other hand, we hope to introduce more substitution diversity into the cyclic products. After the domino Michael−Michael reaction of **2** and 1 equiv of a β-aryl-substituted enal was complete, from which intermediate **B**, depicted in Scheme 1, would be generated, excess crotonaldehyde was added to continue the cascade Michael−aldol sequences. Such a tandem one-pot, three-component reaction was successful, and better results were obtained when substrate **2a** was applied. The fused carbocycles **3l**−**p** were directly isolated in excellent stereoselectivities, while the yields were fair due to more possible reaction pathways (entries 11−15).

It was pleasing that the in situ generated intermediate **B** could be also applied in a highly diastereoselective Michael addition−Henry reaction with nitroolefins.[8a] As illustrated

Scheme 2. Synthetic Expansion of the Domino Michael−Michael Intermediate



(12) For the synthesis of multifunctional substrates **2**, see the Supporting Information.

(13) Substrates **2** with electron-withdrawing groups on the oxindole motif are unstable, and destruction occurs even at room temperature.

in Scheme 2, the one-pot, three-component tandem reaction of substrate **2a**, cinnamaldehyde, and β-nitrostyrene smoothly afforded the fused and spiro carbocycle **4** with eight contiguous chiral centers in an enantiopure form.

In conclusion, we have designed a new type of multifunctional synthons, (*E*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoates **2**. They have been successfully applied in a three-component, domino Michael−Michael−Michael−aldol process with two molecules of α,β-unsaturated aldehydes under quadruple iminium−enamine−iminium−enamine catalysis. A spectrum of enantiomeric hydroindane derivatives, bearing six contiguous stereocenters and a spirooxindole motif, were delivered in a highly economic and effective manner. Moreover, their one-pot, three-component tandem reaction with α,β-unsaturated aldehydes and nitroolefins was accessible, and a complex polycyclic framework with up to eight contiguous chiral centers has been assembled with remarkable efficacy. Currently, more synthetic applications and transformations are underway in our laboratory.

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Supporting Information Available: Experimental procedures, structural proofs, NMR spectra, HPLC chromatograms of the products, X-ray data of enantiopure **3h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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