ORGANIC LETTERS

2012
Vol. 14, No. 21
5590–5593

Direct Catalytic Enantioselective Vinylogous Aldol Reaction of α-Branched Enals with Isatins

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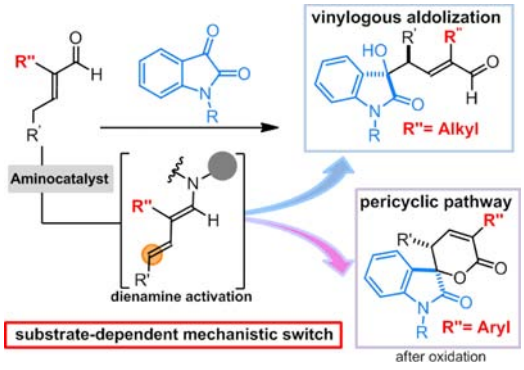
Received October 2, 2012

ABSTRACT



The direct vinylogous aldol reaction of α-substituted α,β-unsaturated aldehydes with isatins is described. The chemistry provides easy access to valuable 3-substituted 3-hydroxyoxindole derivatives with high stereocontrol and perfect γ-site selectivity. Preliminary mechanistic studies suggest that, depending on the nature of the α-branched enal substituents, two divergent reaction mechanisms can be operating, leading to different products and stereochemical outcomes.

The aldol reaction is one of the most powerful C−C bond-forming technologies in the synthetic repertoire.[1] Its synthetic power has been increased recently by its successful marriage to the principle of vinylogy.[2] The vinylogous aldol reaction[3] uses α-enolizable α,β-unsaturated carbonyl substrates as "extended dienolates" to directly construct densely adorned δ-hydroxylated α,β-unsaturated carbonyls. These functional arrays are common structural motifs in biologically relevant natural molecules, in particular within polyketide structures.[4] This has provided the impetus for developing highly stereoselective, catalytic, vinylogous aldol reactions,[4] their direct application in the total synthesis of natural products attesting to their utility.[5] These methods mainly rely upon indirect Mukayama-type strategies, which require the preformation of stable dienolate equivalents.

The direct in situ activation of unmodified carbonyl substrates has recently been recognized as the ultimate goal in further expanding the synthetic potential and atom economy of this chemical transformation. Despite recent advances in direct addition procedures, only cyclic compounds, i.e. 2(5*H*)-furanone derivatives, have found application in asymmetric catalytic vinylogous aldol processes.[6] In contrast, the use of acyclic unsaturated carbonyls is to date limited to a single strategy where the direct vinylogous

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(3) For a comprehensive review, see: Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.
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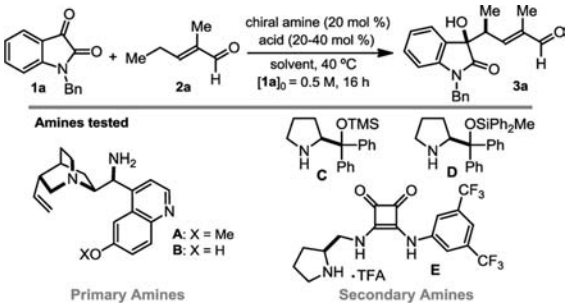
10.1021/ol302711w
Published on Web 10/18/2012

aldol reaction is integrated at the beginning of a cascade sequence, the aldol step being followed by an intramolecular *oxa*-Michael reaction.[7] Herein, we describe the successful realization of a discrete vinylogous aldol reaction with an unmodified acyclic unsaturated carbonyl substrate that is not implemented within a cascade sequence. We have found that α-substituted enals **2** directly react with isatins **1** upon in situ activation by a chiral secondary amine catalyst through dienamine formation. The chemistry secures direct access to products **3** with high stereocontrol and perfect γ-site selectivity. Notably, these are complex scaffolds, in which two biologically relevant molecular elements are combined: a δ-hydroxyl-α,γ-dialkyl-α,β-unsaturated unit[8] linked to an oxindole framework.[9]

Our initial investigations focused on the addition of (*E*)-2-methylpent-2-enal **2a** to *N*-benzyl protected isatin **1a** (Table 1). The choice of the model reaction was motivated by our interest in devising versatile strategies for stereoselectively accessing 3-substituted 3-hydroxyoxindole derivatives[10] and our previous experiences with vinylogous reactivity.[11] We have recently established how the cinchona-based primary amine catalysts **A** and **B**[12] can induce vinylogous nucleophilicity within a substitution reaction manifold. They can activate α-substituted enals **2** toward an S_N1-type γ-alkylation pathway by means of a transiently generated dienamine intermediate.[11a] This persuaded us to test these primary amine catalysts in the aldol addition reaction. Despite extensive efforts, we have not succeeded in translating the α-branched enal/cinchona-based catalyst system to the vinylogous aldol process. The use of 20 mol % of catalyst **A** or **B** led to **3a** as the unique product, but with a poor stereocontrol (entries 1 and 2 in Table 1). The quest for a more stereoselective system prompted us to undertake an extensive catalyst screening (details given in Tables S1−S2). This led to an unexpected

Table 1. Development of the Direct Vinylogous Aldolization of α-Branched Enals with Isatins[a]



entry	amine	acid	solvent	conv (%)[b]	dr[b]	ee (%)[c]
1	**A**	TFA	$CHCl_3$	42	6:1	<5
2	**B**	TFA	$CHCl_3$	67	2.8:1	42
3	**C**	BA	toluene	35	1:1	40
4[d]	**E**	–	CH_2Cl_2	<5	–	–
5	**C**	BA	EtOH	>95	1.2:1	75
6	**D**	BA	EtOH	>95	1.2:1	83
7[e]	**D**	BA	EtOH	>95	1.4:1	89
8[e]	**D**	BA	MeCN	30	3:1	92
9[e]	**D**	BA	MeCN/EtOH[f]	49	2.7:1	92
10[e]	**D**	CF_3-BA	MeCN/EtOH[f]	59	3.2:1	91
11[e,g]	**D**	CF_3-BA	MeCN/EtOH[f]	87[f]	3.2:1	90

[a] BA: benzoic acid; CF_3-BA: 2,6-bis(trifluoromethyl)benzoic acid. Catalyst **A** and **B** were used with 2 equiv of TFA, while **C** and **D** required a 1:1 combination with the acid. Reactions on a 0.05 mmol scale using 2 equiv of **2a**. [b] Both conversion and dr were determined by ^1H NMR analysis of the crude reaction mixture. [c] Ee value of the major diastereomer, as determined by HPLC analysis. [d] 1 equiv of *N,N*-diethylacetamide (DEA) was used to improve the solubility of **E** (see ref 15). Reaction conducted with $[\mathbf{1a}]_0 = 0.25$ M and adding 2.8 equiv of H_2O. [e] Reaction at 25 °C. [f] Reaction in a 9:1 MeCN/EtOH mixture. [g] 10 mol % of amine **D** and of CF_3-BA. Reaction time: 40 h; $[\mathbf{1a}]_0 = 2$ M. Yield value refers to the isolated compound after chromatography.

observation: the commercially available diphenylprolinol silyl ether **C**[13] could indeed catalyze the vinylogous aldol process (entry 3). This stands in contrast to the catalytic profiles of secondary amines that are generally unable to efficiently activate sterically hindered carbonyl compounds, such as α,β-disubstituted enal of type **2a**.[14] Interestingly, the bifunctional squaramide-based aminocatalyst **E** did not promote the model vinylogous aldol reaction.[15]

Despite the moderate level of stereoselectivity initially achieved with catalyst **C**, we were encouraged by the unanticipated power of secondary amine catalysis to direct the reaction manifold toward a γ-site selective aldolization through dienamine activation of α-branched enals.[16] Examination of the reaction media revealed that the catalytic process was greatly influenced by polarity, with solvents

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(13) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(14) The activation of α-branched enals generally requires chiral primary amines; see: (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (b) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892. Chiral secondary amines have found limited applications only in the iminium ion activation of highly reactive α-branched acroleins; see: (c) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, *45*, 1956. (d) Bondzic, B. P.; Urushima, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 5434. For the sole examples dealing with the iminium ion activation of α,β-disubstituted enals, see: (e) Deiana, L.; Dziedzic, P.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Cordova, A. *Chem.—Eur. J.* **2011**, *17*, 7904. (f) E.-M. Tanzer, E.-M.; Zimmer, L. E.; Schweizer, W. B.; Gilmour, R. *Chem.—Eur. J.* **2012**, *18*, 11334.

(15) Albrecht, Ł.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543.

(16) An analog of catalyst C (the 3,5-trifluoromethyl aryl substituted derivative) has been used to promote the asymmetric γ-amination of linear unsubstituted enals via dienamine activation; see: Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. It was proposed that this reaction proceeded through a peculiar pericyclic mechanism.

Table 2. Scope of the Direct Vinylogous Aldolization[a]

entry	R^1	R^2	R^3	R^4	**3**	yield (%)[b]	dr[c]	ee (%)[d]
1	Me	Me	H	H	**a**	87(47)	3.2:1	90(76)
2	Bn	Me	H	H	**b**	68	2.5:1	95(77)
3	CH_2-SMe	Me	H	H	**c**	89	1.6:1	94(70)
4	CH_2NHCbz	Me	H	H	**d**	63	3:1	94(74)
5[e]	Bn	Bn	H	H	**e**	65	1.5:1	90(78)
6[e]	Et	Et	H	H	**f**	28[f]	1.5:1	94
7	Me	Me	Cl	H	**g**	92	1.7:1	86(73)
8	Bn	Me	Cl	H	**h**	69(35)	1.6:1	92(78)
9	Me	Me	Br	H	**i**	68	1.9:1	85(78)
10	Me	Me	Me	H	**j**	76(44)	3.8:1	92(81)
11	Me	Me	NO_2	H	**k**	87	1.5:1	87(75)
12	Me	Me	CF_3O	H	**l**	71	2.9:1	89(63)
13	Me	Me	Me	Me	**m**	65	3.9:1	91(77)
14	Me	Me	H	Br	**n**	88	2.4:1	92(71)

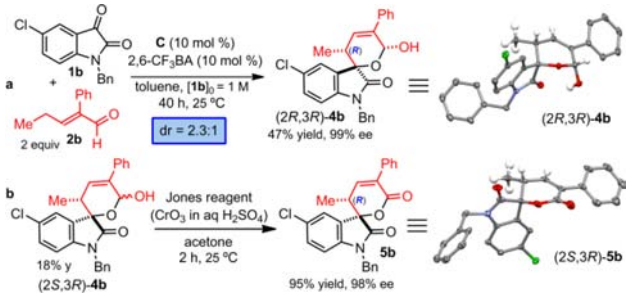
[a] Reactions performed on a 0.2 mmol scale using 2 equiv of **2**. *E*/*Z* ratio of **2**: >95:5; no double bond scrambling was observed during the catalytic reaction. Only the (*E*)-isomer of the aldol products **3** was detected. [b] Yield of the isolated product **3** after chromatographic purification on silica gel. Values between brackets (entries 1, 8, 10) refer to the yield of the isolated major diastereomer of the alcohols obtained after $NaBH_4$ reduction of compounds **3**. [c] Determined by ^{1}H NMR of the crude mixture. [d] Ee value of the major diastereomer, as determined by HPLC analysis. Values between brackets refer to the ee's of the minor diastereomers of **3**. [e] 20 mol % of catalyst **D** was used. [f] Yield of the isolated major diastereomer of **3f**.

with a high dielectric constant strongly increasing both reactivity and stereoselectivity (entries 5–8). Gratifyingly, the stereocontrol was also sensitive to catalyst structural modifications, the bulkier silyl protective group of catalyst **D** leading to a significant improvement (compare entries 5 and 6).[17] A second cycle of optimization using catalyst **D** established a 9:1 acetonitrile/ethanol mixture as the best reaction medium, while revealing that the nature of the acidic additives was also crucial for modulating catalyst efficiency (entries 9 and 10). The use of a 1:1 combination of amine **D** (10 mol %) and 2,6-bis(trifluoromethyl) benzoic acid and a more concentrated reaction system ($[\mathbf{1a}]_0 = 2$ M) provided the product **3a** with synthetically useful results over a 40-h reaction time and at rt (entry 11: **3a** isolated in 87% yield, 3.2:1 dr, and 90% ee). These conditions were selected to evaluate the scope of the vinylogous aldol process.

As reported in Table 2, different substituents, including heteroatom-containing moieties, can be accommodated at the enal γ-position without affecting the site selectivity, while slightly increasing the enantioselectivity of the vinylogous aldol process (ee up to 95%, entries 2–4). More encumbered aliphatic substituents in the α-position are well-tolerated (entries 5–6). Concerning the scope of isatin

(17) Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. *Helv. Chim. Acta* **2009**, *92*, 1225.

Scheme 1. ORTEP Drawing at 50% Probability[18]



derivatives **1**, different substitution patterns were well-tolerated, regardless of their electronic properties (entries 7–14). Although the vinylogous aldolization proceeds with poor to moderate control over the relative configuration, it is possible to easily isolate, by simple chromatography, the two diastereoisomers upon simple $NaBH_4$ reduction of adducts **3**. This testifies to the synthetic utility of the process. Proof-of-concept has been provided for the alcohol derivatives obtained from **3a**, **3h**, and **3j** (entries 1, 8, and 10). The absolute and relative configuration for the major diastereoisomer of compound **3h** was determined by anomalous dispersion X-ray crystallographic analysis: an (*S*) absolute configuration at the newly formed γ-stereocenter was inferred.[18]

We then carried out further explorations to fully delineate the reaction scope. Unexpectedly, the presence of an aryl substituent at the α-branched enal position led to a different product distribution. As depicted in Scheme 1a, reacting (*E*)-2-phenylpent-2-enal **2b** with isatin **1b** in toluene in the presence of catalyst **C** gave rise to the formation of the spirooxindole lactol **4b**. Despite the moderate level of relative stereocontrol (2.3:1 ratio), both diastereoisomers were formed in enantiomerically pure form and isolated as a single stereoisomer after chromatography. Simple oxidation of the minor (2*S*,3*R*)-**4b** isomer granted access to the spirooxindole dihydropyran-2-one **5b** (Scheme 1b). X-ray analyses[18] established an (*R*) absolute configuration at the γ-stereocenter for both the diastereomeric products **4b**, in contrast with the stereochemistry observed in products **3**.

Intrigued by these observations, we carried out preliminary mechanistic investigations to understand the origin of the divergent pathways, which led to different products and opposite stereochemical outcomes. We used NMR spectroscopic analyses to gain information on the conformational behavior of the dienamine intermediate **I** (Figure 1a). When mixing the aminocatalyst **C** with enal **2a** or **2b** (bearing a methyl or a phenyl α-branched substituent, respectively) in toluene-d_8 and in the presence of 4 Å molecular sieves, the corresponding dienamine intermediate **I** was formed (see Figures S1–S10 for details). Interestingly, the nature of the α-branched substituent did not alter the conformational preference of **I**, as the *s-trans*

(18) Crystallographic data for compounds **3h**, (2*R*,3*R*)-**4b**, (2*S*,3*R*)-**5b**, and **7** are available free of charge from the Cambridge Crystallographic Data Centre, accession numbers CCDC 885390, CCDC 885391, CCDC 885392, and CCDC 885695, respectively.

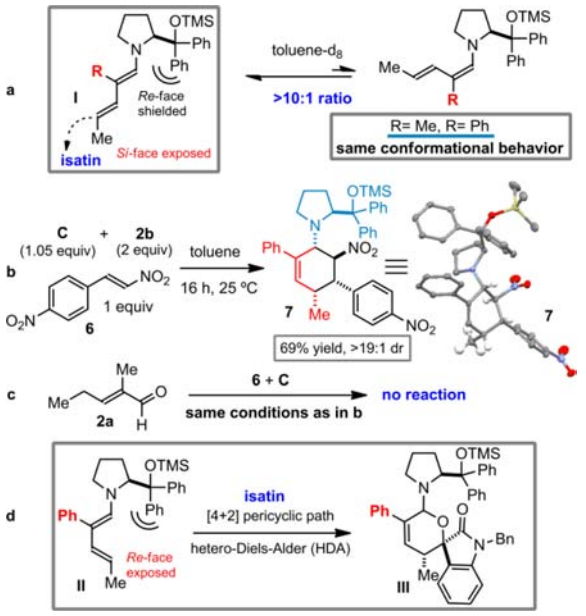


Figure 1. Mechanistic investigations.

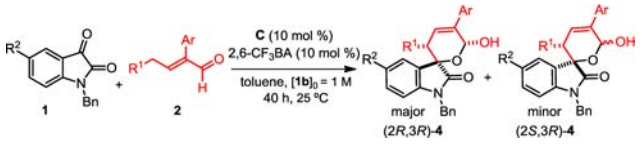
dienamine with the same geometry of the two double bonds is the more stable species in both cases. The classical "steric control approach" generally invoked to rationalize the stereochemical outcome of a process catalyzed by **C**[13] is consistent with the sense of asymmetric induction observed when using an α-alkyl substituted enal of type **2a** (chemistry reported in Table 2). Indeed, the efficient shielding by the chiral fragment in **C** determines the selective engagement of the isatin **1** with the *Si* face of the dienamine intermediate **I** (Figure 1a). In contrast, this model, which is based on the direct addition of isatin from the unshielded face of **I**, cannot account for the (*R*)-absolute configuration of the γ-stereocenter observed for products **4**.

The striking difference in the stereochemistry between products **3** and **4**, in spite of the similar ground state thermodynamic stability of the intermediates **I**, led us to consider that a mechanistically distinct pathway may be operative for enal **2b**. In analogy with related studies by Jørgensen and colleagues on the γ-functionalization of linear enals via dienamine activation,[16] we envisaged a pericyclic [4 + 2] cycloaddition pathway. To test this hypothesis, the two different enal substrates **2a** and **2b** were individually mixed with the catalyst **C** and the nitrostyrene derivative **6**, a dienophile that can react in concerted pericyclic processes catalyzed by amine **C**.[19] While the enal bearing a methyl substituent remained totally unreacted (Figure 1c), aldehyde **2b** led to the fast and quantitative formation of the Diels–Alder-type product **7** with perfect stereocontrol (Figure 1b).[20] After chromatographic purification, the cyclic adduct **7** was characterized by X-ray crystallographic analysis.[18]

(19) (a) Talavera, G.; Reyes, E.; Vicario, J. L.; Carillo, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 4104. (b) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212.

(20) The presence of a phenyl substituent raises the HOMO energy of electron-rich dienes; see: Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569.

Table 3. HDA-Type Reaction To Access Spiroxindoles[a]



entry	R^1	Ar	R^2	**4**	yield (%)[b] major/minor	dr[c]	ee (%)[d] major/minor
1	Me	Ph	H	**a**	45/22	2.2:1	99/99
2	Me	Ph	Cl	**b**	47/18	2.3:1	99/98
3[e]	Me	Ph	Me	**c**	63/19	3.0:1	99/98
4[e]	Me	Ph	NO_2	**d**	45/31	1.3:1	99/97
5[e]	Et	Ph	H	**e**	36/–	2.2:1	99/–
6[e]	Me	4-Cl-C_6H_4	H	**f**	69/22	3.2:1	99/98

[a] Reactions performed on a 0.2 mmol scale using 2 equiv of **2**. *E*/*Z* ratio of **2**: >95:5; no double bond scrambling was observed under the reaction conditions. [b] Yield of the isolated diastereomerically pure compounds (2*R*,3*R*)-**4** and (2*S*,3*R*)-**4**, which can be separated by chromatography. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] 20 mol % of **C**.

Although an extensive mechanistic investigation is still needed, some preliminary interpretation is possible. The initial observations are in agreement with a hetero-Diels–Alder (HDA) process being operative with enal **2b**, bearing a phenyl α-substituent. A simple rotation around the C–C single bond of dienamine **I**[16] would produce intermediate **II**, having the required *s-cis* geometry to engage in a pericyclic path (Figure 1d). The HDA process with isatin would result in the labile hemiaminal ether intermediate **III**, which can easily hydrolyze to the lactol product **4** while releasing the catalyst **C**. It is to be noted that the stable cyclic adduct **7** in Figure 1b is not amenable to this hydrolysis event.

The HDA-type reaction of α-aryl substituted enals and isatins provides direct access to valuable spirocyclic oxindole scaffolds, which are found in a large number of natural and unnatural compounds.[9] We therefore explored the synthetic potential of this catalytic asymmetric approach. As reported in Table 3, the reactions proceed readily at rt, and quantitative conversion is obtained at convenient reaction times. Both the diastereoisomers of the spirolactols **4** can be individually isolated in almost enantiomerically pure form.

This work offers a rare example of a discrete catalytic and enantioselective vinylogous aldol reaction of an unmodified acyclic unsaturated carbonyl substrate.

Acknowledgment. Research support from the ICIQ Foundation, MICINN (Grant CTQ2010-15513), and the European Research Council (Starting Grant no. 278541—ORGA-NAUT to P.M.) is gratefully acknowledged.

Supporting Information Available. Complete experimental procedures, compound characterization, HPLC traces, and NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.