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Ionic Nucleophilic Catalysis of Chiral Ammonium Betaines for Highly Stereoselective Aldol Reaction from Oxindole-Derived Vinylic Carbonates

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Supporting Information

ABSTRACT: A new strategy for developing stereoselective bond-forming reactions is introduced; it takes advantage of the ionic nucleophilic catalysis of chiral ammonium betaines to utilize vinylic esters simultaneously as the enolate precursor and the acylating agent for coupling with electrophiles. Its synthetic utility is clearly demonstrated by the realization of a highly diastereo- and enantioselective aldol reaction from oxindole-derived vinylic carbonates.

Vinylic esters (carbonates) represent one of the universal structural motifs encountered in natural products and are important, reactive synthetic intermediates.[1−3] The primary structure of a vinylic ester comprises activated ester and electron-rich olefin moieties (Figure 1). While the activated

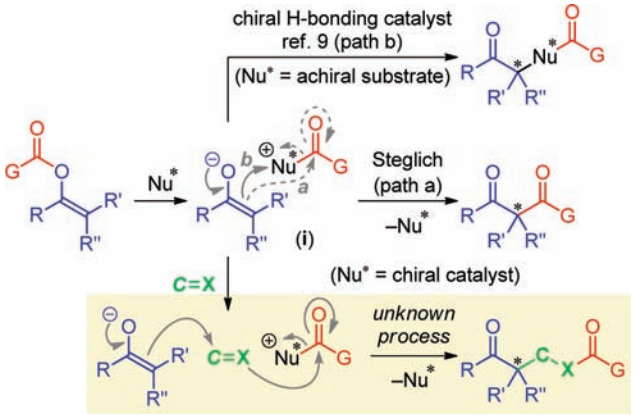


Figure 1. Working hypothesis (G = alkyl, alkoxy).

ester component of vinylic esters has been widely used as a mild and efficient acylating reagent,[2] the olefin component has been comparatively underutilized in organic synthesis except for use as a monomer in the preparation of several polymers and copolymers in academia and industry.[3] In the arena of asymmetric catalysis, the latent reactivity of the olefin component has been harnessed for the effective utilization of vinylic esters as enolate precursors or surrogates in facilitating otherwise difficult stereoselective bond-forming reactions.[4−7] Among the synthetically valuable transformations based on this strategy, chiral nucleophilic catalyst-mediated, enantioselective Steglich-type rearrangements are unique in regard to realizing the simultaneous utilization of the acyl and enolate moieties of substrates such as 5-oxazolyl carbonates (Figure 1 middle).[8−10] These reactions involve the generation of chiral enolate **i** through the attack of the catalyst (Nu*) on vinylic esters (carbonates) and subsequent stereoselective acyl transfer within the ion pair **i**. Recently, Seidel and co-workers discovered that use of a nucleophilic reaction partner such as isoquinoline for the generation of **i** from an azlactone-derived vinylic carbonate under the influence of a chiral hydrogen-bonding catalyst enabled the stereoselective introduction of the nucleophile framework into the product (Figure 1 top).[9] On the other hand, if external electrophiles (C═X) such as carbonyl compounds or electron-deficient olefins could be inserted into **i** to forge two new bonds in a sequential manner, the potential utility of the asymmetric nucleophilic catalysis would be greatly expanded (Figure 1 bottom). However, this possibility remains unexplored, probably because of the difficulties associated with precise control of the reactivity of **i** and the stereochemistry of the initial C−C bond formation by the catalyst.[11] Herein we report our own approach to address this problem using the characteristic features of chiral ammonium betaines **1** as ionic nucleophilic catalysts,[8h,12] leading to the development of a highly diastereo- and enantioselective aldol reaction from oxindole-derived vinylic carbonates. The key for establishing this new system is the appropriate structure and reactivity of aryl carbonates of type **I** possessing an ammonium enolate (Figure 2), which enables selective enolate addition to the aldehyde and subsequent acyl transfer. Thus, the stereochemically homogeneous product is derivatized with judicious incorporation of the two functional groups originating from the vinylic carbonate.

As illustrated in Figure 2, the reaction of chiral ammonium betaine **1** with vinylic ester **2** smoothly generates the intermediate **I**, and the following pseudo-intramolecular attack of this transient enolate on the aryl ester moiety of the pairing ammonium ion gives the usual Steglich product (path A). However, considering the moderate acyl transfer ability of the ammonium ion, we envisaged that ammonium enolate **I** could react with an external electrophile such as aldehyde **3** to afford the corresponding ammonium alkoxide **II** (path B), which would rapidly be O-acylated to furnish the fully protected aldol adduct **4** with regeneration of the betaine catalyst **1**. We further expected that this unique catalytic pathway involving

Received: March 8, 2012
Published: April 6, 2012

   dx.doi.org/10.1021/ja3022939 | J. Am. Chem. Soc. 2012, 134, 6972−6975

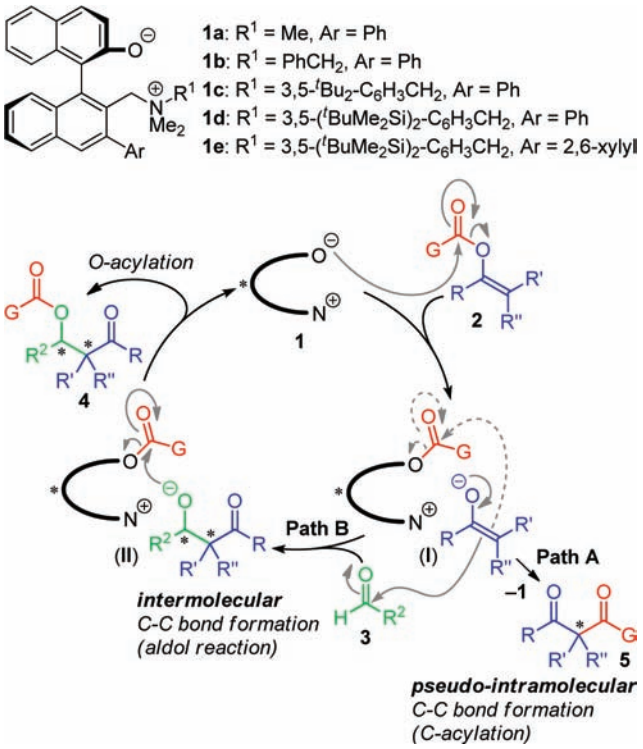
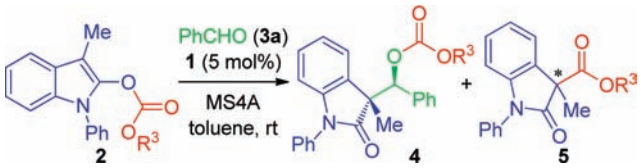


Figure 2. Structures of chiral ammonium betaines **1** and the mechanism of their catalysis with vinylic esters.

intermolecular C−C bond formation could be selectively guided by the appropriate structural modification of **1**. To examine this hypothesis, 3-substituted oxindole-derived vinylic carbonate **2** was selected as a model substrate. Although the oxindole core and the related structural frameworks, particularly those having a quaternary carbon stereocenter, are commonly found in biologically relevant molecules,[13] the catalytic asymmetric aldol reaction of oxindoles has been poorly studied, and only a few protocols using highly reactive carbonyl compounds as requisite electrophiles have been developed.[14] This is probably because the aldol adducts of oxindoles are relatively unstable under basic conditions and are prone to retro-aldol reactions. In fact, Bencivenni and co-workers recently pointed out this problem and introduced an O-protection procedure for ease of analysis and eventual product manipulations.[14d] In this respect, our approach would be intrinsically advantageous for the in situ derivatization of the desired aldol adduct in a stable form.

The actual investigation was initiated by carrying out the reaction of *O*-trichloroethoxycarbonyl enolate **2a** with benzaldehyde (**3a**) in the presence of chiral ammonium betaine **1a** and 4A molecular sieves (MS4A) in toluene.[15] Nearly complete consumption of the starting **2a** was observed within 30 min, and the desired aldol adduct **4a** was obtained as a 6:1 mixture of diastereomers in 77% yield with concomitant yet considerable formation of the Steglich product **5a** (**4a**:**5a** = 8:1). The enantiomeric excess of the major isomer of **4a** was determined to be 34% ee (Table 1, entry 1). As anticipated, structural modification of the catalyst had a beneficial impact on the product distribution as well as on the stereoselectivity, and interestingly, installation of the 3,5-disubstituted benzyl group on the nitrogen atom of **1** dramatically enhanced the production of **4a** over **5a** with promising diastereo- and enantioselectivities (entries 3 and 4). The aromatic substituent on the binaphthyl backbone (Ar) also affected each selectivity, and the 2,6-xylyl group was found to be optimal (entry 5).[16] In addition, we reasoned that the structure of the carbonate substituent of **2** (R^3) would be critical for the improvement of the reaction profile because the parent structure of **1** is modified by the acyl transfer from **2** to serve as a chiral component of the ammonium enolate in the C−C bond-forming stage (Figure 2, **I** → **II**). Indeed, the incorporation of the benzyl group (**2b**) improved the enantioselectivity to 92% ee, albeit with a decrease in the catalyst turnover (entry 6). Additional electronic tuning by the introduction of a trifluoromethyl substituent (**2c**) delivered sufficient reaction efficiency and even higher selectivities (entry 7). Eventually, the use of 3,5-bis(trifluoromethyl)benzyl-substituted **2d** in combination with the catalyst **1e** led to virtually complete discrimination of the reaction pathway with excellent levels of stereoselectivity (entry 8). Importantly, the attempted reaction

Table 1. Optimization of the Conditions for the Aldol Reaction of Vinylic Carbonates 2 with Benzaldehyde (3a) Catalyzed by Chiral Ammonium Betaines 1[a]



entry	1	R^3	2	yield (%)[b]	dr[c]	4:5[c]	ee (%)[d]	4
1	**1a**	Cl_3CCH_2	**2a**	77	6:1	8:1	34	**4a**
2	**1b**	Cl_3CCH_2	**2a**	67	7:1	4:1	39	**4a**
3	**1c**	Cl_3CCH_2	**2a**	79	15:1	15:1	71	**4a**
4	**1d**	Cl_3CCH_2	**2a**	82	15:1	11:1	78	**4a**
5	**1e**	Cl_3CCH_2	**2a**	86	≥20:1	13:1	89	**4a**
6[e]	**1e**	$PhCH_2$	**2b**	51	≥20:1	≥20:1	92	**4b**
7	**1e**	4-CF_3−$C_6H_4CH_2$	**2c**	88	≥20:1	≥20:1	93	**4c**
8	**1e**	3,5-$(CF_3)_2$−$C_6H_3CH_2$	**2d**	89	≥20:1	≥20:1	95	**4d**

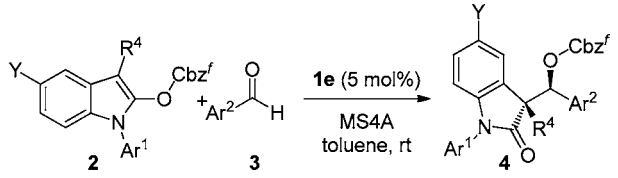
[a]Unless otherwise noted, reactions were performed on a 0.1 mmol scale with 2.0 equiv of **3a** and 5 mol % **1** in toluene (2.0 mL) for 0.5 h at rt. [b]Isolated yields. [c]The diastereomeric ratios and product distributions were determined by ^{1}H NMR (400 MHz) analysis of crude aliquots. [d]Shown is the enantiomeric excess of the major isomer as determined by chiral stationary phase HPLC. The absolute configurations of **4a**−**d** were assigned by analogy to **4e** (Scheme 1). [e]The reaction time was 12 h.

dx.doi.org/10.1021/ja3022939 | *J. Am. Chem. Soc.* 2012, 134, 6972−6975

of **2d** with 4-dimethylaminopyridine (DMAP) (5 mol %) as a representative nucleophilic catalyst under otherwise identical conditions exclusively yielded the corresponding Steglich product **5d** (12 h, 96% yield), illustrating the distinct feature of the ionic nucleophilic catalysis of chiral ammonium betaines of type **1**.[17]

With the optimized conditions in hand, further experiments were conducted to explore the scope of this new stereoselective aldol reaction of oxindoles catalyzed by **1e**. As shown by the representative results summarized in Table 2, the present system nicely accommodated a range of simple aromatic aldehydes, and the corresponding aldol adducts were obtained uniformly with excellent diastereo- and enantioselectivities (entries 1−5). Moreover, heteroaromatic aldehydes appeared to be good candidates for an electrophilic partner (entries 6 and 7). The structure of vinylic carbonates **2** could also be varied with regard to the C(5) and C(3) substituents without loss of stereocontrol (entries 8−11). It should be noted that comparable reactivity and selectivity were observed in the reaction with vinylic carbonate **2i** bearing a *p*-methoxyphenyl group on the nitrogen atom (entry 12).

Table 2. Substrate Generality [Cbz^f = 3,5-$(CF_3)_2$-$C_6H_3CH_2$][a]



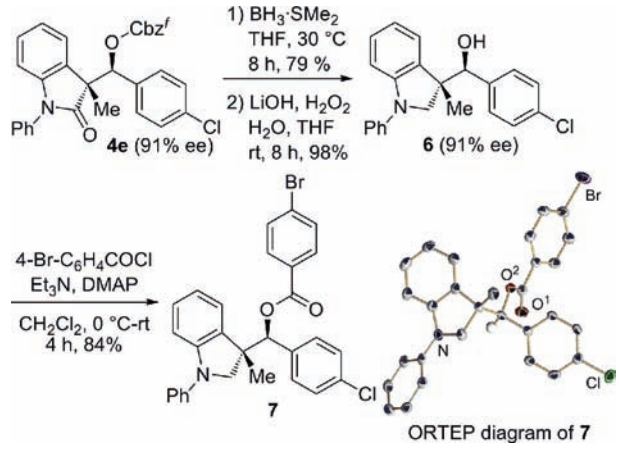
2d: R^4 = Me, Y = H, Ar^1 = Ph **2g**: R^4 = Et, Y = H, Ar^1 = Ph
2e: R^4 = Me, Y = Br, Ar^1 = Ph **2h**: R^4 = Bn, Y = H, Ar^1 = Ph
2f: R^4 = Me, Y = MeO, Ar^1 = Ph **2i**: R^4 = Me, Y = H, Ar^1 = PMP

entry	2	Ar^2 (3)	yield (%)[b]	dr[c]	ee (%)[d]	4
1	**2d**	4-ClC_6H_4 (**3b**)	96	≥20:1	91	**4e**
2	**2d**	4-MeC_6H_4 (**3c**)	87	≥20:1	96	**4f**
3	**2d**	3-BrC_6H_4 (**3d**)	95	14:1	90	**4g**
4	**2d**	3-$MeOC_6H_4$ (**3e**)	90	≥20:1	93	**4h**
5	**2d**	1-naphthyl (**3f**)	73	≥20:1	95	**4i**
6	**2d**	3-pyridyl (**3g**)	92	10:1	92	**4j**
7	**2d**	2-thienyl (**3h**)	91	≥20:1	96	**4k**
8	**2e**	**3a**	90	≥20:1	96	**4l**
9	**2f**	**3a**	87	≥20:1	94	**4m**
10	**2g**	**3a**	89	18:1	92	**4n**
11	**2h**	**3a**	87	18:1	92	**4o**
12	**2i**	**3a**	94	≥20:1	93	**4p**

[a]Reactions were performed on a 0.1 mmol scale with 2.0 equiv of **3** and 5 mol % **1e** in toluene (2.0 mL) for 0.5 h at rt. [b]Isolated yields. [c]The diastereomeric ratios were determined by ^{1}H NMR (400 MHz) analysis of crude aliquots. [d]Shown is the enantiomeric excess of the major isomer as determined by chiral HPLC analysis. The absolute configuration of **4e** was determined by X-ray crystallographic analysis of its derivative (Scheme 1; see the Supporting Information for details). Absolute configurations of **4f−p** were assigned by analogy to **4e**.

The absolute configuration of **4e** was determined by X-ray crystallographic analysis after it was converted into the corresponding indoline derivative **7** (Scheme 1). Reduction of the carbonyl moiety of **4e** by treatment with BH_3·SMe_2 in THF followed by hydrolysis using LiOOH afforded secondary alcohol **6**. Subsequent acylation with 4-bromobenzoyl chloride furnished a good yield of **7**, which was recrystallized from an *n*-hexane/EtOH solvent system at room temperature (see the ORTEP diagram in Scheme 1).

Scheme 1. Determination of the Absolute Configuration of 4e and the ORTEP Diagram of 7 (H Atoms except Those Attached to the Stereogenic Carbon Have Been Omitted for Clarity)



In conclusion, we have introduced a new strategy for developing stereoselective carbon−carbon bond-forming reactions that exploits the salient features of chiral ammonium betaines as ionic nucleophilic catalysts to utilize the binary reactivity of vinylic esters (carbonates) for coupling with electrophiles. This enables a highly stereoselective aldol reaction of oxindole-derived vinylic carbonates with simple aldehydes. The present approach significantly expands the scope of asymmetric ionic nucleophilic catalysis of chiral ammonium betaines and also offers an unprecedented opportunity to utilize both of the reactive subunits of vinylic esters in reaction development.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Representative experimental procedures, physical data for all new compounds, details of X-ray analysis, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NEXT program, the Global COE Program in Chemistry of Nagoya University, the Program for Leading Graduate Schools "Integrative Graduate Education and Research Program in Green Natural Sciences" at Nagoya University, and Grants for Scientific Research from JSPS. K.K. acknowledges financial support from JSPS.

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(15) The addition of MS4A was crucial to avoid protonation of the reactive ammonium enolate by a small amount (<5%) of water, which was contaminated from slightly hygroscopic onium salt **1**.

(16) The molecular structure of the optimal catalyst **1e** was unequivocally determined by single-crystal X-ray diffraction analysis. See the Supporting Information for details.

(17) When tetrabutylammonium β-naphthoxide (5 mol%) was employed as a representative intermolecular ion-pairing nucleophilic catalyst in the reaction of **2d** with **3a** at room temperature, only a trace amount of the aldol adduct **4d** was detected by ^{1}H NMR analysis of a crude aliquot.