Evaluation of the Relationship between the Catalyst Structure and Regio- as well as Stereoselectivity in the Chiral Ammonium Bifluoride–Catalyzed Asymmetric Addition of Silyl Nitronates to α,β-Unsaturated Aldehydes

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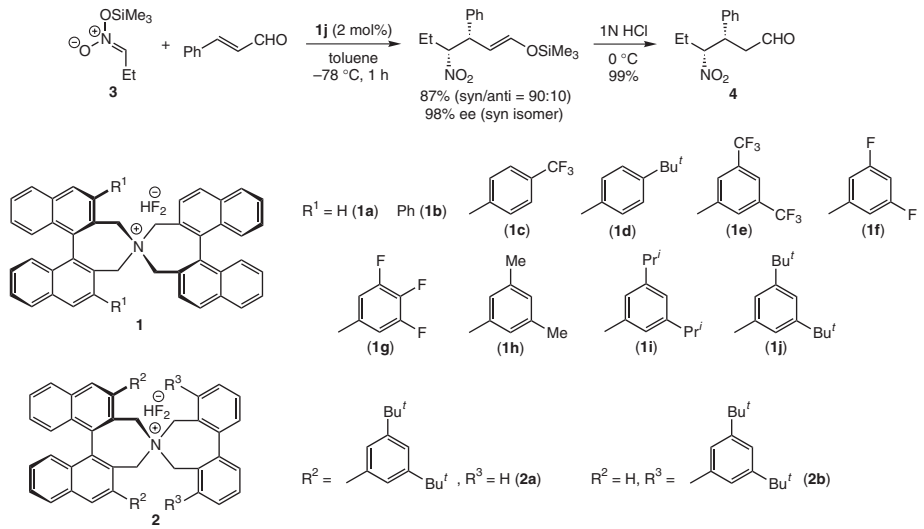
Unique relationship between the catalyst structure and regio- and stereoselectivity in the chiral quaternary ammonium bifluoride–catalyzed asymmetric addition of silyl nitronates to α,β-unsaturated aldehydes has been reported.

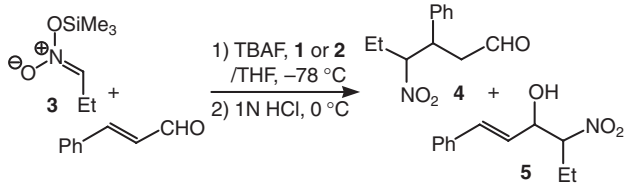
We recently disclosed highly enantioselective Michael addition of silyl nitronates to α,β-unsaturated aldehydes catalyzed by designer chiral quaternary ammonium bifluoride **1j** under mild conditions, offering direct access to both optically active γ-nitro aldehydes and their enol silyl ethers as exemplified in Scheme 1.[1,2] The success of this asymmetric Michael reaction heavily relied on the appropriately modified structure of the catalyst, which played a key role in primarily leaving the aldehyde carbonyl intact and at the same time controlling the stereochemistry of two newly created adjacent stereogenic carbon centers through the formation of chiral ammonium nitronate. This observation prompted us to make a thorough evaluation of the relationship between the structure of chiral quaternary ammonium bifluoride and the regio- and stereoselectivity of the addition of silyl nitronates to enals. In this letter, we wish to describe the results of this study, uncovering the crucial elements for establishing the fluoride–catalyzed asymmetric Michael addition of silyl nitronates to α,β-unsaturated aldehydes.

We chose the addition of trimethylsilyl nitronate **3**[3] derived from nitropropane to *trans*-cinnamaldehyde as a representative reaction system, and examined the effect of the catalyst structure on the regio- and stereoselectivity. Initially, the reaction of **3** with *trans*-cinnamaldehyde was conducted using 5 mol % of tetrabutylammonium fluoride (TBAF) as catalyst in THF at −78 °C, which afforded a mixture of 1,4-adduct **4** and 1,2-adduct **5** in a ratio of 1.4:1 (89% combined yield) after treatment with 1 N HCl, and the *syn*/*anti* ratio of **4** was revealed to be 55:45 (Entry 1 in Table 1). With this information at hand, we then attempted the reaction with chiral quaternary ammonium bifluoride **1a**[4] (2 mol %) under otherwise identical conditions[5] and, surprisingly, observed lowered 1,4-selectivity with slightly improved diastereoselectivity (Entry 2). Although certain asymmetric induction was attained for both *syn* and *anti* isomers, this result indicated that it was not solely the rigid *N*-spiro structure created by the two simple chiral binaphthyl subunits that delivered the significant alteration of the regiochemical preference. Even use of **1b**[4] having phenyl group at 3,3′-position of one binaphthyl unit (R^1) as catalyst provided similar results (Entry 3), and further electronic and steric modification by the introduction of trifluoromethyl (**1c**)[6] and *tert*-butyl (**1d**) substituents at *para* position of the 3,3′-phenyl group, respectively, had only a minor effect on both regio- and stereoselectivity (Entries 4 and 5). Interestingly, however, dramatic improvement of 1,4-selectivity was achieved when **1e**[1,7] possessing 3,5-bis(trifluoromethyl)phenyl group as R^1 was used as catalyst and the enantiomeric excess of *syn*-**4** was enhanced to 90% ee (Entry 6). This phenomenon could not be accounted for by mere electronic effect, because the reactions under the influence of 3,5-difluorophenyl- and 3,4,5-trifluorophenyl–substituted **1f** and **1g**,[4] respectively, resulted in the substantial decrease of 1,4-selectivity (Entries 7 and 8). While the results of an additional investigation using catalyst **1h**[8] with 3,5-dimethylphenyl group seemed to support the contribution of an electron-withdrawing property of the trifluoromethyl substituent (Entry 9), the considerable jump in regio- and stereoselectivity with introduction of isopropyl group in



Scheme 1.

Table 1. Effect of the catalyst structure on the regio- and stereoselectivity of chiral ammonium bifluoride–catalyzed asymmetric addition of silyl nitronate **3** to *trans*-cinnamaldehyde[a]



Entry	Catalyst	Yield[b] (%)	**4**/**5**[c]	*syn*/*anti* of **4**[c–e]	% ee of **4** (config)[e,f]	
					syn (3*S*,4*R*)	*anti*
1	TBAF	89	1.4:1	55:45		
2	**1a**	99	1.1:1	69:31	39	31
3	**1b**	99	1.1:1	66:34	37	35
4	**1c**	99	2.4:1	70:30	52	48
5	**1d**	99	1.9:1	68:32	41	41
6	**1e**	98	16:1	76:24	90	52
7	**1f**	99	3.1:1	66:34	41	12
8	**1g**	99	2.4:1	66:34	38	11
9	**1h**	99	2.4:1	67:33	33	19
10	**1i**	98	10:1	76:24	88	59
11	**1j**	99	19:1	76:24	94	74
12	**2a**	95	3.2:1	52:48	66	48
13	**2b**	75	1:3.5	70:30	25	5

[a]The reaction was carried out with 1.2 equiv. of **3** in the presence of TBAF (5 mol %), **1** or **2** (2 mol %) in THF (0.1 M substrate concentration) at −78 °C for 1–1.5 h followed by treatment with 1 N HCl at 0 °C. [b]Combined isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Diastereomeric ratio of **4**. [e]Relative and absolute stereochemistries of major *syn*-**4** were established by X-ray crystallographic analysis of its acetal with (2*R*,3*R*)-2,3-butanediol.[11] [f]Enantiopurity was determined by GLC analysis using a chiral column [Astec Chiradex G-TA (30 m × 0.25 mm)].

place of methyl substituent (**1i**) strongly suggested the importance of a steric demand of the trifluoromethyl group (Entry 10). Indeed, the highest 1,4-selectivity and enantioselectivity were attained by the employment of **1j**[1,9] having 3,5-di-*tert*-butylphenyl group as catalyst (Entry 11), which confirmed the prime value of a sterically hindered substituent rather than electron-withdrawing one specifically at 3,5-position of the 3,3′-phenyl group for controlling the regio- and stereochemistry of the present addition.

Based on the results of this survey by varying the 3,3′-aromatic substituents, we finally evaluated the contribution of the binaphthyl structure particularly in association with 3,5-di-*tert*-butylphenyl substituent. Unexpectedly, replacing the simple chiral binaphthyl moiety of **1j** by achiral biphenyl (**2a**) ruined the regioas well as stereoselectivity (Entry 12), and switching the catalyst to **2b** consisting of a simple chiral binaphthyl unit and an achiral biphenyl one with the requisite 3,5-di-*tert*-butylphenyl group at 3,3′-position led to the preferential formation of 1,2-adduct **5** (Entry 13). The present unique observation clearly showed the crucial importance of the harmony of the primary *N*-spiro structure with two chiral binaphthyl subunits and 3,3′-phenyl group with bulky 3,5-substituents. This criterion, together with the beneficial solvent effect provided by toluene in this case, appeared essential to establish highly enantioselective Michael addition of silyl nitronates to α,β-unsaturated aldehydes, and should be further appreciated in the development of other asymmetric Michael addition processes based on this approach.[10]

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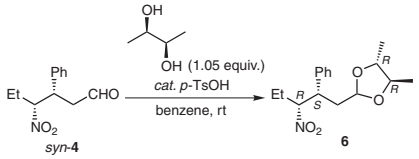
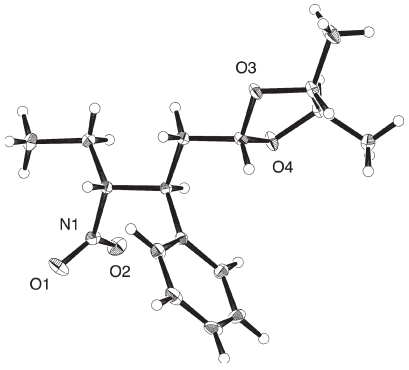
11 The acetal **6** was recrystallized from diethyl ether/hexane. Crystal structure data for **6** collected at 123 K: $C_{16}H_{23}NO_4$, $M_w = 293.36$, orthorhombic, space group $P2_12_12_1$, $a = 9.4834(7)$ Å, $b = 9.4378(7)$ Å, $c = 21.375(1)$ Å, $V = 1576(1)$ Å^3, $Z = 4$, $D_{calcd} = 1.236$ g/cm^3, $R_1 = 0.034$.





ORTEP diagram of **6**. Solvent molecules are omitted for clarity.

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