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Asymmetric Conjugate Addition of Silyl Enol Ethers Catalyzed by Tethered Bis(8-quinolinolato) Aluminum Complexes

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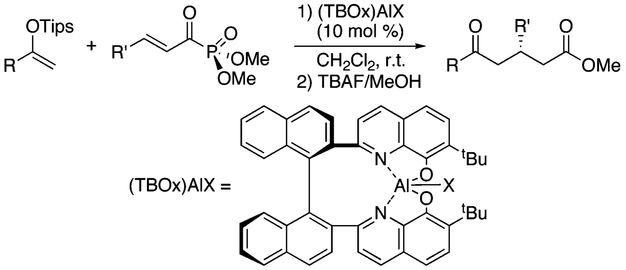
The Lewis acid-promoted conjugate addition of silylketene acetals and silyl enol ethers to α,β-unsaturated carbonyl derivatives, the Mukaiyama−Michael (MM) reaction,[1] is an attractive alternative to the conventional metalloenolate process owing to a mild reaction condition and frequently superior regioselection (1,4- in preference to 1,2-addition).[2] Catalytic asymmetric variants of this process have received extensive attention and continue to be powerful carbon−carbon bond forming reactions since these methods provide synthetically useful enantioenriched 1,5-dicarbonyl synthons.[3,4] Whereas various catalysts developed for the MM reaction have centered on the use of silylketene acetals, silyl enol ethers[3g−j,s,4a,c] have received relatively little attention in the context of asymmetric catalysis. This deficiency in the aforementioned reaction may arise, in part, from the decreased nucleophilicity of silyl enol ethers in comparison to that of silylketene acetals. It is described herein that a new chiral tethered bis(8-quinolinolato) (TBOx) aluminum(III) complex effectively catalyzed the highly enantioselective MM reaction of silyl enol ethers, including tetrasubstituted enolates that provided access to enantiomerically enriched all-carbon quaternary centers.[5,6]

On the basis of promising stereoselectivity displayed by an enantiopure TBOx ligand recently developed in our laboratory for the catalytic asymmetric pinacol coupling reaction,[7] the possible utility of this ligand in the enantioselective conjugate addition reaction was explored.[8] After brief screening of metal salts, TBOxH was found to react cleanly with diethylaluminum chloride and provided the corresponding aluminum chloride complex. While this aluminum chloride complex (Table 1, entry 1) was not catalytically active, activation by AgOTf or AgSbF$_6$ provided a highly reactive species, presumably the cationic aluminum complex[9] (entries 2 and 3).[10] Although the rate of the reaction catalyzed by (TBOx)AlOTf was noticeably slower than that of the reaction catalyzed by the corresponding hexafluoroantimonate complex, both catalysts were highly enantioselective. Even the encumbering phenyl substituent on a Michael acceptor did not adversely affect the yield or enantioselectivity (entry 4). The same trend was observed for a range of silyl enol ethers (entries 5−10).

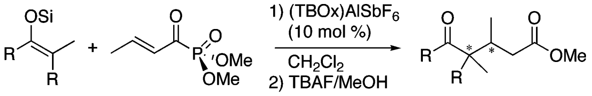
Table 1. (TBOx)AlX Catalyzed Mukaiyama−Michael Reaction

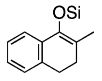
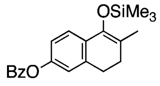
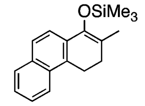
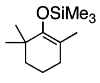
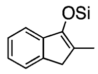


entry	X	R	R′	time (h)	yield (%)	ee (%)
1	Cl	Ph	Me	36	trace	N/D[a]
2	TfO	Ph	Me	24	70	98
3	SbF$_6$	Ph	Me	12	77	97
4	SbF$_6$	Ph	Ph	12	86	96
5[b]	SbF$_6$	*p*-BrPh	Me	12	83	98
6[b]	SbF$_6$	*p*-BrPh	Ph	12	76	98
7[b]	SbF$_6$	Cy	Me	12	77	99
8[b]	SbF$_6$	Cy	Ph	12	69	98
9	SbF$_6$	*i*-Pr	Me	12	70	98
10[b]	SbF$_6$	*i*-Pr	Ph	12	66	98

[a] Not determined. [b] The absolute configuration was not determined.

Table 2. Syntheses of Enantio-Enriched All-Carbon Quaternary Stereocenters



entry	Michael donor		temp. (°C)	yield (%)	d.r.	ee(%)[a]
1		Si = SiMe$_3$	r.t.	59	6:1	96
2		Si = Si(OEt)$_3$	0	56	>30:1	99
3			r.t.	87	7:1	96
4			r.t.	97	8:1	96
5			r.t.	54	>30:1	80
6		Si = SiMe$_3$	r.t.	84	1.7:1	99
7		Si = Si(OEt)$_3$	0	84	3.4:1	99

[a] Values are the ee of a major diastereomer. Those of minor isomers were 50, 83, 81, 58, N/D, 79, and 72%, respectively.

Having successfully developed an effective catalyst for the conjugate addition of simple silyl enol ethers, the possibility of using sterically demanding tetrasubstituted enolates was investigated. The latter Michael donors would give rise to enantioenriched carbonyl products bearing α-quaternary stereocenters, whose preparation by catalytic means remains largely an unsolved, albeit highly important, problem.[5,6] To our delight, a range of tetrasubstituted trimethylsilyl enol ethers underwent the MM reaction and formed all-carbon quaternary stereocenters with high enantioselectivities (Table 2).[11] Diastereoselectivities and yields varied from moderate to high ranges.[12] Interestingly, triethoxy silyl enol ethers[13] (entries 2 and 7) were found to be more reactive than corresponding trimethyl silyl enol ethers (entries 1 and 6). The former nucleophiles underwent smooth conjugate addition reaction at 0 °C, leading to increased diastereoselectivities. To our knowledge, the present

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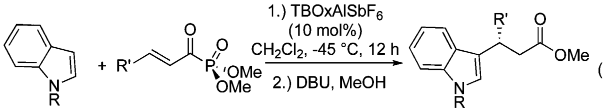
method represents the only catalytic asymmetric MM reaction that provides access to enantioenriched α-carbonyl all-carbon-substituted quaternary stereocenters.

Evans et al. reported that pybox−scandium(III) triflate complexes catalyzed the conjugate addition of indoles to α,β-unsaturated acyl phosphonates with excellent yields and enantioselectivities (indole Friedel−Crafts alkylation (FCA) reaction).[14,15] Thus it was of interest to us whether our catalyst was also capable of promoting the above reaction since the indole skeleton is an important substructure in both natural products and therapeutic agents[15b] (eq 1). *N*-Benzylindole readily reacted with both crotonyl (83% yield, 95% ee) and cinnamoyl (85% yield, 98% ee) phosphonates.[16] It is noteworthy that the catalyst turned over with the same level of efficiency in both MM and indole FCA reactions. The catalyst was regenerated by silyl transfer in the former case, but by proton transfer in the latter case.



(eq. 1)

R = H, R' = Me, 30% yield, 58% ee; R = Me, R' = Me, 99% yield, 88% ee
R = Bn, R' = Me, 83% yield, 95% ee; R = Bn, R' = Ph, 85% yield, 98% ee

The model that could rationalize the sense of absolute stereoinduction of the present MM reaction (Table 1) is provided in Figure 1.[17] The direct product, silyl enol phosphonate, was obtained as a single geometric isomer (>30:1 *E*/*Z*, ^{1}H NMR), which implicates a *s-cis* acyl phosphonate conformation.[3h] Placement of the phosphonate oxygen in the sterically more crowded apical position should be favored as the P−O bond is longer than the C═O bond.[18] The addition of a nucleophile from the indicated *s-cis* enoate diastereoface should predominate on the basis of resident nonbonding interactions. The absolute stereochemistry observed in the indole FCA reaction (eq 1) could also be accounted for by this model.

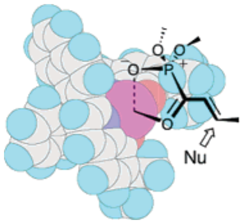


Figure 1. Model of [Al(TBOx)(crotonylphosphonate)]$^+$ complex.

In summary, a new chiral aluminum-based Lewis acid, (TBOx)AlSbF$_6$ proved to be a highly enantioselective catalyst for the Mukaiyama−Michael reaction of simple silyl enol ethers, as well as tetrasubstituted silyl enol ethers that gave rise to enantioenriched α-carbonyl all-carbon-substituted quaternary stereocenters. This catalyst was also shown to be a viable alternative to catalysts reported for the indole Friedel−Crafts alkylation reaction.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds, and crystallographic data; X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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