Chiral Triarylcarbenium Ions in Asymmetric Mukaiyama Aldol Additions

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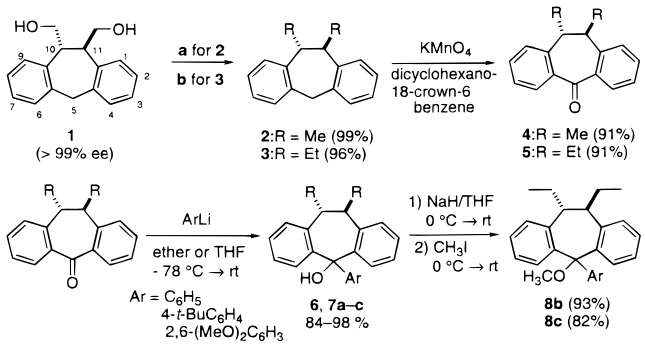
The Mukaiyama aldol reaction is one of the most versatile synthetic methods for stereoselective carbon−carbon bond formation. Asymmetric catalysis of this category utilizing chiral complexes derived from B, Al, Sn(II), Ti(IV), Cu(II), Pd(II), and Ln(III) has been explored in the past 10 years with significant breakthroughs.[1] Mukaiyama and co-workers have documented novel uses of various trityl salts serving as efficient catalysts in various aldol type transformations,[2] highlighting their potential in asymmetric variations. Nevertheless, several intrinsic and pending problems still hinder their practical design in that context. First, the reacting carbenium ion center is sp^2-hybridized. Placement of the three flanking aryl groups in a chiral environment is so far impossible due to the extremely low barrier to racemization of chiral carbenium ions.[3] Second, in sharp contrast to most existing chiral Lewis acids generated from chiral natural sources (e.g., diols, diamines, amino acids, and tartrates),[1,4] no natural skeleton has been found that is relevant to the triarylmethyl scaffold. Third, the precise nature of the catalytic species in these transformations remains elusive in view of the recent elegant mechanistic study by Bosnich.[5] Apparently, development of new types of chiral Lewis acids with reactive *carbenium-based* centers are essential in view of their potential impact on both mechanistic and synthetic utility aspects. We describe herein our preliminary findings toward this end.

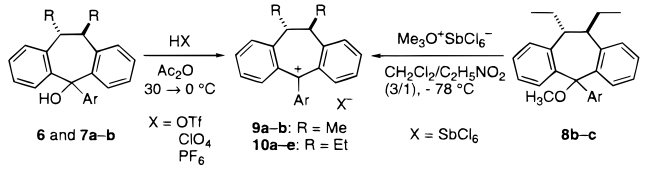
Platzek and Snatzke have reported the synthesis of C_2-symmetric diol **1**, a common skeleton in various anti-inflammatory drugs, in scalemic form.[6] This resolved (10*R*,11*R*)-**1**, was utilized as a conceivable trityl ion precursor, whose enantiomeric purity was determined to be >99% enantiomeric excess (ee) by HPLC analysis on a chiral support (Chiralcel OJ). We have so far accessed two different 10,11-dialkyl (dimethyl and diethyl) substituted C_2-symmetric trityl salts. To convert the alcohol moieties into methyl appendages, the diol-**1** was mesylated with methanesulfonyl chloride (MsCl) in CH_2Cl_2 in the presence of Et_3N (6 equiv). Reduction of the resultant dimesylate with $LiEt_3BH$ (3 equiv) in anhydrous THF provided 10,11-dimethyldibenzosuberane (**2**) in essentially quantitative yield (Scheme 1). In a similar manner, the scalemic diol **1** was transformed in 96% yield to the corresponding ditosylate by treatment with TsCl in the presence of Et_3N and catalytic 4-(dimethylamino)pyridine (DMAP). Double S_N2 displacement

Scheme 1[a]



(a) Key: (**a**) (i) $MsCl/Et_3N/CH_2Cl_2$, (ii) $LiBEt_3H$/THF, 0 °C → rt; (**b**) (i) $TsCl/Et_3/N/CH_2Cl_2$, cat. DMAP, (ii) Me_2CuLi/ether, −10 °C.

Scheme 2



of the ditosylate with $(CH_3)_2CuLi$ at −10 °C provided the diethyl analog **3** quantitatively.[7] These two dialkyldibenzosuberanes were readily oxidized at ambient temperature to the respective ketones, **4** and **5**, by $KMnO_4$ (2.5 equiv) in benzene using dicyclohexano-18-crown-6 as a phase transfer catalyst.[8] Both ketones were obtained in 91% yields.

To probe the stereoelectronic influence of the 5-aryl group on the structure, reactivity, and selectivity of triarylcarbenium ions in the aldol process, two representative aryl appendages (*tert*-BuC_6H_4 and 2,6-$(MeO)_2C_6H_3$) were selected in addition to the parent phenyl group.[9] The requisite trityl alcohols, **6** and **7a**−**c**, were prepared in 84−98% yields by aryllithium addition to the respective dibenzosuberones.[10]

Independent treatment of 1-aryldibenzosuberols, **6** and **7a**,**b** (Ar = Ph and 4-*tert*-butylphenyl), with an appropriate acid (HX) in the presence of a water scavenger (acetic anhydride) allowed the preparation of the corresponding chiral trityl salts, **9a**,**b** and **10a**−**c**, with three different counter ions (TfO^-, ClO_4^-, and PF_6^-).[11] In all cases, the reddish orange salts could be obtained in good yields (80−98%) by gradual addition of cold diethyl ether into the reaction media at 0 °C to induce crystallization (Scheme 2). In some instances, these highly moisture- and heat-sensitive materials can even be obtained in analytically pure form (i.e., **9b** and **10a**), allowing for unambiguous determination of composition. The 2,6-dimethoxy substituted trityl alcohol **7c** was not amenable to the Dauben procedure[11] (HX/Ac_2O) due to the extreme solubility of the resulting trityl salts in acetic anhydride. The final targeted hexachloroantimonates, **10d** (Ar = 4-*tert*-BuC_6H_4) and **10e** (Ar = 2,6-$(MeO)_2C_6H_3$), could only be generated in situ by a Meerwein salt-promoted ionization of the appropriate trityl methyl ethers (**8b** and **8c**), recently developed in our laboratories.[9] The requisite methyl ether precursors were formed in 93% (**8b**) and 82% (**8c**) yields, respectively, by the standard Williamson etherification (NaH/CH_3I) of the corresponding alcohols (Scheme 1).[12]

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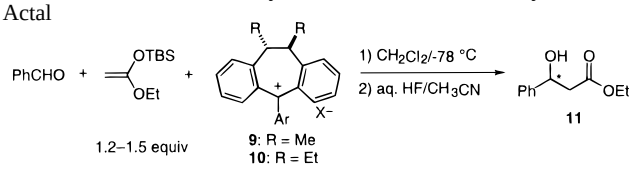
Table 1. Chiral Triarylcarbenium-Ion-Mediated Mukaiyama Aldol Addition between Benzaldehyde and Acetate-Derived Silyl Ketene Actal



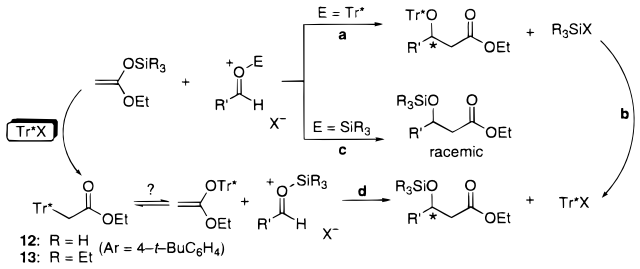
entry	Ar	X (catalyst)	time (h)	yield (%)[a]	ee (%)[b]	config.[c]
1	C_6H_5	OTf (**9a**)	3	75	3	*S*
2	C_6H_5	ClO_4 (**9b**)	6	92	12	*S*
3	C_6H_5	ClO_4 (**10a**)	3	52	24 (4[d])	*R*
4	C_6H_5	ClO_4 (**10a**)	4.5	67	16	*R*
5	C_6H_5	ClO_4 (**10a**)	6	99	11	*R*
6	C_6H_5	ClO_4 (**10a**)[e]	3	22	50	*R*
7	4-*tert*-BuC_6H_4	ClO_4 (**10b**)	3	40	38 (27[d])	*R*
8	4-*tert*-BuC_6H_4	PF_6 (**10c**)	3	20	32 (19[d])	*R*
9	4-*tert*-BuC_6H_4	$SbCl_6$ (**10d**)	4	48	6 (8[d])	*R*
10	2,6-$(MeO)_2C_6H_3$	$SbCl_6$ (**10e**)	4	53	22	*R*

[a] Isolated yields. [b] Determined by HPLC analysis on Chiralcel OD column. [c] Correlated by the optical rotation of the corresponding acid with the literature value. [d] From the aldol reaction with TMS ketene acetal. [e] One equivalent of catalyst was added.

Our targeted aldol addition involves the slow addition of *O*-ethyl silyl ketene acetal (SKA) to benzaldehyde with catalytic chiral trityl salts (10−20 mol %) at −78 °C. This most challenging scenario was found to proceed smoothly, leading to enantiomerically enriched ethyl 3-hydroxy-3-phenylpropionate (**11**) in good yields after protodesilylation of the inital silylated aldolate (Table 1).

The extent and sense of asymmetric induction were highly dependent on silyl substituents, counterions,[2b] steric bulk of R groups, substitution pattern on the pending aromatic rings, and reaction time. The use of trimethylsilyl (TMS) ketene acetal consistently led to a lower level of asymmetric induction in the aldol process as compared with the *tert*-butyldimethylsilyl (TBS) analog. Best results were achieved by the employment of trityl perchlorates (**10a**,**b**) and hexafluorophosphate (**10c**). The free β-hydroxy ester **11** was obtained with enantioselectivities of up to 38%. A significant drop in enantioselectivity (entries 1 and 9) was observed in the triflate (**9a**) and hexachloroantimonate (**10d**) presumably due to the facile intervention of silyl and $SbCl_5$ catalysis, respectively.[9,13] Both 10,11-dimethyl- and -diethyl-substituted trityl perchlorates, **9b** and **10a**, effectively catalyze the aldol reaction leading to **11** in >92% yields with a similar magnitude of enantiocontrol. However, a complete reversal in the sense of asymmetric induction was observed (entries 2 and 5).[14,15] Trityl salts containing the 4-*tert*-butylphenyl group uniformly led to higher enantioselectivities as compared with the parent (Ar = Ph) analogs (entries 3, 7, and 8). It should be pointed out that gradual decoloration of triarylcarbenium ions was observed in most instances. However, upon addition of extra SKA, the aldol reaction still proceeded with prolonged reaction time (6 h) (entries 3−5). The chemical yield was increased by 47% (from 52% to 99%) with a concomitant drop in the enantiomeric excess of **11** to half of its original value (from 24% to 11%). These results indicate that trityl ions were gradually consumed presumably due to slow methathesis between tritylated aldolates and R_3SiX.[16] Under such circumstances, silyl catalysis completely took over once the trityl ions were tied up. To evaluate the extreme asymmetric discrimination with our devised chiral template, one full equivalent of trityl perchlorate **10a** was used in this model aldol addition. The β-hydroxy ester **11** was obtained in 50% ee, albeit with significant diminution of chemical yields from 52% to 22% (entries 3 and 6).

Scheme 3



The production of scalemic β-hydroxy ester **11** in the chiral carbenium-ion-mediated aldol process strongly suggest that a trityl-ion-catalyzed pathway originally proposed by Mukaiyama[2] is operable to some extent (path **a**, Scheme 3). For an efficient regeneration of the chiral catalyst, the exchange process between the tritylated aldolate and the released R_3SiX (path **b**) must have a faster rate than that of the R_3SiX-catalyzed reaction (path **c**). An alternative reaction pathway would involve an initial exchange between the silyl group on *O*-ethyl SKA and the trityl ion to give a chiral *O*-trityl ketene acetal followed by a R_3SiX-catalyzed aldol reaction (path **d**). Similarly, this exchange process has to be faster than path **c** to secure asymmetric generation of the aldol product.

Two independent lines of evidence led to the exclusion of the last mechanistic scenario. First, instead of observing any *O*-trityl ketene acetal formation, only trace amount of *C*-trityl acetate **13** was produced when *O*-ethyl SKA was mixed with an equal amount of chiral trityl perchlorate **10a** at −78 °C.[17] The *C*-trityl acetate formation became more significant when the reaction was warmed to the ambient temperature. Second, treatment of the independently prepared *C*-trityl acetate, **12** (R = H) or **13** (R = Et), with benzaldehyde (1 equiv) in the presence of TBSOTf or $TBSClO_4$ under similar aldol conditions provided no trityl alcohols or aldol products. This result rules out any possible electrophile-promoted C → O trityl transfer to reform the trityl ketene acetal.

In conclusion, we have documented *the first example of asymmetric Mukaiyama aldol additions mediated by chiral triarylcarbenium ions*, albeit with significant intervention of the unproductive silyl catalysis. Searches for a better chiral trityl ion candidate that can adopt a more rigid conformation and exhibit a more reactive carbenium ion center are currently underway.

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Supporting Information Available: Preparation and full spectroscopic characterization of **2**−**6**, **7a**−**c**, **8b**−**c**, **9b**, **10a**, and **11**−**13** (23 pages). See any current masthead page for ordering and Internet access instructions.

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(14) The absolute configuration of the β-hydroxy ester **11** was determined by comparison of the optical rotation of the corresponding acid with the literature value. Boaz, N. W. *J. Org. Chem.* **1992**, *57*, 4289.

(15) X-ray crystallographic analysis of **7c** shows highly inhomogeneous packing of both conformers (unpublished results). This unexpected opposite sense of asymmetric induction may be attributed to a facile equilibration between two trityl ion conformations with the 10,11-dimethyl substituents diaxially and diequatorially disposed. See also: Vedejs, E.; Erdman, D. E.; Powell, D. R. *J. Org. Chem.* **1993**, *58*, 2840.

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