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Brønsted Acid-Catalyzed Insertion of Aryldiazoacetates to sp² Carbon–CHO Bond: Facile Construction of Chiral All-Carbon Quaternary Center

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C-C bond insertion reaction has attracted much attention in the synthetic community as an ideal means of realizing truly efficient organic transformations. In addition to the direct activation of a C-C bond by the aid of transition metal catalysts,¹ the formal C-C bond insertion reaction, in which the skeletal rearrangement of the initially generated unstable intermediate is involved, seems to be a highly attractive method for the expeditious synthesis of complex molecules.²

During the course of our study on the use of diazoacetates in acid catalysis,³ we became aware of the reaction of ethyl diazoacetate and aldehydes providing α -formyl ester, reported by Hossain and Kanemasa independently.⁴ Namely, under the influence of a proper acid catalyst, ethyl diazoacetate reacts with the acid activated arylaldehyde to generate diazonium intermediate **A**, which then rearranges by the migration of aryl group to give the one-carbon homologated aldehyde (path *a*). The whole process can be considered as a formal insertion of methylenecarboxylate to the sp² C–CHO bond. Since the migration of hydride to the diazonium carbon is also a feasible process providing β -keto ester (path *b*), careful examination of the C–C bond insertion product.⁵



Stimulated by this research and our recent finding regarding the use of α -aryldiazoacetates in acid catalysis,^{3c} we assumed that addition of α -aryldiazoacetates to aldehydes would lead to the formation of α , α -disubstituted- α -formyl esters by the judicious choice of acid catalysts.⁶ As chiral auxiliary can be introduced at the ester moiety of diazo compounds, asymmetric induction at the all-carbon quaternary center might be also anticipated.^{7,8}

To prove this concept, some acid catalysts were initially screened in the reaction of benzaldehyde and *tert*-butyl phenyldiazoacetate (Scheme 1). The reaction catalyzed by BF₃•Et₂O provided the expected *tert*-butyl α, α -diphenyl- α -formyl ester 1 in moderate yield concomitant with some amounts of undesired α -phenyl- β -keto ester 2. Use of aluminum Lewis acid led to the increased ratio of β -keto ester. The reaction catalyzed by TiCl₄ was sluggish at -78 °C. To our delight, TfOH was found to be a suitable catalyst, providing the aldehyde 1 in good yield accompanied by only a small amount of β -keto ester 2.

Encouraged by this successful implementation of the formal C-C bond inserton of phenyldiazoacetate to the aldehyde, our focus then moved to the asymmetric induction at the newly formed all-carbon quaternary center by the introduction of a chiral auxiliary on the ester moiety of phenyldiazoacetate (Table 1). Commercially avail-

Scheme 1. Evaluation of Acid Catalysts



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	4-tolyI-CHO + Ph CO ₂ R N ₂	(20 mol %) solvent -78 °C, 30 min	4-tolyl * CHO Ph CO ₂ R	
entry	R	solvent	yield (%) ^b	dec
1	\frown	CH_2Cl_2	88	47
2	Ph	toluene	61	22
3	(–)-menthyl	CH_2Cl_2	42	22
4	-	toluene	11	20
5	(–)-phenyl- menthyl	CH_2Cl_2	74	32
6		toluene	55	>95
7^d		toluene	74	>95

^{*a*} Reactions were performed with *p*-tolualdehyde (0.24 mmol) and phenyldiazoacetate (0.20 mmol) in the presence of 20 mol % TfOH. ^{*b*} Isolated yield. ^{*c*} Determined by the ¹H NMR of the crude reaction mixture. ^{*d*} Performed with 5 equiv of aldehyde (1.0 mmol).

able (–)-*trans*-2-phenyl-1-cyclohexanol, (–)-menthol, and (–)phenylmenthol were selected as key chiral components,^{9,10} and TfOH-catalyzed reaction of the corresponding phenyldiazoacetate and 4-tolualdehyde was surveyed. Consequently, the superiority of phenylmenthyl ester became obvious by performing the reaction in toluene, providing the essentially single diastereomer of α -phenyl- α -(4-tolyl)- α -formyl ester in 55% yield (entry 6). An additional investigation revealed the use of 5 equiv of the aldehyde optimal (entry 7). In all of the experiments above, the amount of β -keto ester was suppressed to less than 10% yield.

With this optimized condition in hand, the scope of this C–C bond insertion was investigated as shown in Table 2. Use of 3- or 2-tolualdehyde could lead to the inserted product in moderate yields with exclusive diastereoselectivities, regardless of the severe steric hindrance around the quaternary center generated in the case of 2-tolualdehyde. The reaction could also be applied to the aldehydes bearing electron-donating or withdrawing group (entries 3 and 4). Further investigation on the use of α,β -unsaturated aldehydes bearing two β -substituents unraveled the feasibility of such a transformation, providing α -alkenyl- α -aryl- α -formyl esters in fairly good yields and diastereomeric excesses (entries 5–7). Subsequently, the scope of aryldiazoacetates was examined. Irrespective

Table 2. Stereoselective Insertion of (–)-Phenylmenthyl Aryldiazoacetates to Aldehydes^{*a*}



^{*a*} Reactions were performed with aldehyde (1.0 mmol) and phenylmenthyl aryldiazoacetate (0.2 mmol) in the presence of 20 mol % TfOH (0.040 mmol). ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR of the crude reaction mixture. ^{*d*} Performed at -40 °C. ^{*e*} Performed with 1.2 equiv of aldehyde. ^{*f*} Yield determined after the reduction of the aldehyde.



Figure 1. Ortep representation of (-)-phenylmenthyl α -phenyl- α -(2-tolyl)- α -formyl ester with elipsoids shown at 50% probability level. Hydrogen atoms are omitted for clarity.

of the substituent and substitution pattern, the desired product could be obtained in moderate yields with high stereoinduction. The major limitation we found during this study was the inapplicability of *o*-substituted aryldiazoacetate.

The absolute configuration of the newly generated all-carbon quaternary stereocenter was unambiguously confirmed by X-ray crystallographic analysis of α -phenyl- α -(2-tolyl)- α -formyl ester (Table 2, entry 2) as shown in Figure 1.

The possible pathway that accounts for this observed stereochemistry is shown in Figure 2. The key asymmetric induction step is thought to be the first addition of the electronegative α -carbon of aryldiazoacetate to aldehyde. Effective shielding of one diastereotopic face of aryldiazoacetate might be realized by the phenyl group of the chiral auxiliary. The intermediate diazonium salt would then rearrange into the product via migration of R¹ group of



Figure 2. Possible explanation of the observed stereochemistry.

aldehyde by the inversion of the configuration at the diazonium carbon followed by denitrogenation.

In summary, we have realized the triflic acid-catalyzed formal C–C bond insertion of aryldiazoacetates to aldehydes as a means of constructing an all-carbon quaternary center. Introduction of the phenylmenthyl moiety as chiral auxiliary allowed the facile access to a variety of optically active α , α -disubstituted- α -formyl esters.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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