

Diverse Alkanones by Catalytic Carbon Insertion into the Formyl C–H Bond. Concise Access to the Natural Precursor of Achyrofuran

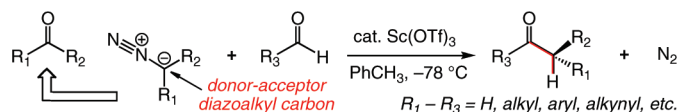
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ABSTRACT



Over a century ago, the first reactions of diazomethane with aldehydes delivered methyl ketones. In the interim, aldehydes have been homologated with trimethylsilyldiazomethane, diazoacetates, and aryldiazomethanes, on rare occasion with catalysis. This work describes a mild procedure for convergent ketone assembly from nonstabilized diazoalkanes, including examples of chiral ketone synthesis with disubstituted (internal) nucleophiles. The method's remarkable tolerance to steric crowding is showcased in a simple approach to achyrofuran, a complex dibenzofuran.

Ketones are prepared chemically by a variety of means, one of the more common being a two-step process involving organometal addition to an aldehyde followed by oxidation. The aldehyde \rightarrow ketone conversion can also be achieved in a single step by reaction with diazo compounds,¹ yet limitations to the scope and efficiency of the reaction are largely unaddressed. Anselme and co-workers have reported benzyl ketone synthesis with aryldiazomethanes in diethyl ether saturated with lithium bromide, but hindered electrophiles such as pivaldehyde failed to react.² Angle and Aggarwal independently developed in situ procedures³ based upon the dual role of alcohol^{3a} or water^{3b} as both a solvent for Bamford–Stevens reaction and a promoter for diazoalkyl insertion, but

desoxybenzoin products were still the focus. In a lone report on catalysis with an Fe(III) salt, competing epoxide formation led to pronounced reductions in chemical yield.⁴ Additionally, and to the best of our knowledge, the use of nonstabilized, internal diazoalkanes for the synthesis of chiral ketones is without precedent.⁵ Herein, we offer a broadly useful protocol for aryl-benzyl, aryl-alkyl, and dialkyl ketone synthesis based on catalytic carbon insertion (see Abstract). The method performs well in functional-

(4) Mahmood, S. J.; Saha, A. K.; Hossain, M. *Tetrahedron* **1998**, *54*, 349–358.

(5) For the conversion of aldehydes to methyl ketones or β -keto esters with TMSCHN₂ and ethyldiazoacetate (respectively), see: (a) Aoyama, T.; Shioiri, T. *Synthesis* **1988**, 228–229. (b) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synlett* **1994**, 521–523. (c) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283–1290. (d) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260. Aryldiazoacetates have been used to prepare α -quaternary aldehydes, but the chiral ketone is just a trace byproduct; see: (e) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434–2435. See also: (f) Dias, E. L.; Brookhart, M.; White, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 2442–2443. (g) Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. *J. Am. Chem. Soc.* **2002**, *124*, 10300–10301.

(6) (a) Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 878–879. (b) Our approach involves modification of two modern protocols for low-temperature hydrazone oxidation. See Supporting Information.

(1) Pioneers in the earliest known reactions of CH₂N₂ and aldehydes were Buchner and Curtius (1885), v. Pechman (1895), Meyer (1905), and Schlotterbeck (1907). For a review, see: Gutsche, C. D. *Org. React.* **1954**, *8*, 364–429. For a modern example, see: Werner, R. M.; Shokek, O.; Davis, J. T. *J. Org. Chem.* **1997**, *62*, 8243–8246.

(2) Loeschorn, C. A.; Nakajima, M.; McCloskey, P. J.; Anselme, J.-P. *J. Org. Chem.* **1983**, *48*, 4407–4410.

(3) (a) Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **2000**, *65*, 6458–6461. (b) Aggarwal, V. K.; de Vicente, J.; Pelotier, B.; Holmes, I. P.; Bonnert, R. V. *Tetrahedron Lett.* **2000**, *41*, 10327–10331.

ized, hindered settings, a fact underscored in a five-step elaboration of the complete carbon framework found in the South American medicinal agent achyrofuran.

Recent work in this laboratory has uncovered both (1) Sc^{3+} as a tunable^{6a} Lewis acidic cation for catalytic carbon insertion with cyclic ketone electrophiles and (2) practical experimental procedures for accessing the requisite mono- and disubstituted diazoalkanes in pure form in solution.^{6b} It appeared of value to extend this mild form of C–C bond construction to aldehyde electrophiles. A study commenced with synthesis of benzyl phenyl ketone from benzaldehyde and phenyldiazomethane (entry 1, Table 1).

Table 1. Aryl-Benzyl Ketones by Sc-Catalyzed Carbon Insertion^a

entry	electrophile	nucleophile	equiv of nucleophile	insertion product	yield (%)
1			1.1		98
2	1a R = H		1.1	2a R = H	97
3	b R = OCH ₃		1.1	b R = OCH ₃	98
4	c R = N(CH ₃) ₂		1.1	c R = N(CH ₃) ₂	91
5	d R = NO ₂		1.1	d R = NO ₂	97
	e R = CF ₃		1.1	e R = CF ₃	
6			1.1		96
7	3a R = OCH ₃		1.1	4a R = OCH ₃	95
8	b R = Cl		1.1	b R = Cl	89
	c R = F		1.1	c R = F	
9			1.1		84
10			1.1		90
11			1.1		82
12			1.1		74
13			2.0		63 ^b
14			1.1		62

^a Conditions: 10 mol % $\text{Sc}(\text{OTf})_3$, -78°C , 0.2 M in toluene; isolated yields after chromatography. ^b Run at -45°C to prevent precipitation of substrate.

Dropwise addition of the nucleophile to a mixture of **1a** and 10 mol % $\text{Sc}(\text{OTf})_3$ in toluene at -78°C resembled a titration, with instantaneous dissipation of the signature red color and N_2 evolution. After workup and filtration through silica gel, **2a** was isolated in 98% yield. There was no detectable union of the reactants in the absence of catalyst, even at 23°C .

As shown in Table 1, the synthesis of desoxybenzoins from aryldiazomethanes and various aryl or heteroaryl aldehydes is quite general. Insertion reactions involving selected electron-donating (OCH_3 or $\text{N}(\text{CH}_3)_2$, entries 2 and 3) or -withdrawing (NO_2 or CF_3 , entries 4 and 5) groups situated *para* to the formyl carbon all proceed smoothly in >90% yield. Such substituents can also be positioned *ortho* (96% yield for *o*- OCH_3 , entry 6), and entries 7 and 8 confirm that halogens are tolerated. The transformation is also effective with pyridine-2-carboxaldehyde (84% of **5**, entry 9) and furfural (90% **6**, entry 10). Given the efficiency and speed of this process, attempts were made to lower the loading of catalyst. If reactions in entries 1, 3, 5, and 8 are carried out with 2 mol % $\text{Sc}(\text{OTf})_3$, the corresponding yields for pure product are 93%, 89%, 81%, and 88%. Importantly, application of carbon insertion to the synthesis of more elaborate (and chiral) ketones is feasible. For instance, thiophene carboxaldehyde **7** engages both an internal diazo compound (**8**, entry 11) or one that is hindered on the basis of *ortho* substitution (**10**, entry 12). Steric crowding in the aldehyde is not a detriment either, as seen by the moderately efficient coupling of mesitaldehyde with methyl phenyl diazomethane (2 equiv, entry 13). Cyclic disubstituted diazomethanes can also be employed; the one-step buildup of acyl indane **15** from electron-rich **14** and 2-bromobenzyldiazomethane is representative (entry 14).

It was of interest next to explore mixed aryl-alkyl and alkyl-alkyl ketone syntheses by appropriate combinations of aldehyde and diazoalkane (Table 2). Reaction of 2-bro-

Table 2. Catalytic Carbon Insertion with Aliphatic Nucleophiles^a

entry	electrophile	nucleophile	equiv of nucleophile	insertion product	yield (%)
1			1.1		74
2			1.1		78
3			1.1		88
4			1.1		77
5			1.1		25 ^b

^a Conditions: 10 mol % $\text{Sc}(\text{OTf})_3$, -78°C , 0.2 M in toluene; isolated yields after chromatography. ^b 55% cinnamyl benzyl ketone was also recovered.

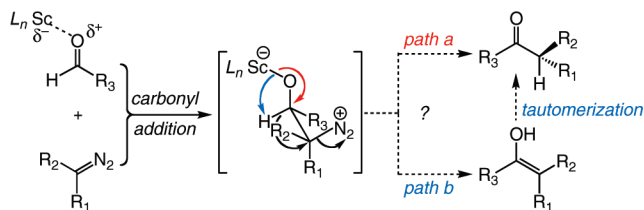
mobenzaldehyde with the potentially labile⁷ cyclopropyl methyl diazomethane (**16**) affords chiral aryl-alkyl product

17 in 74% yield (entry 1). Entry 2 confirms that alkyl-alkyl ketone synthesis is viable for dialkyl diazomethanes and aliphatic electrophiles that are β -branched (78% of **19**). Even pivaldehyde reacts in a coupling that is further noteworthy since neither *trans* \rightarrow *cis* isomerization of the geranial-derived diazo compound **20** nor conjugation of β,γ -unsaturated enone **21** is observed (entry 3). Alkyne-based nucleophiles are also suitable (77% of **23**, entry 4).

The latter result with dihydrocinnamaldehyde as acceptor is a revealing contrast to the outcome in entry 5: reaction of cinnamaldehyde and phenyldiazomethane gives, in addition to the expected ketone, a 25% yield of α -aryl aldehyde **24**. Currently, this is the only substrate for which we have detected competitive C–C (vs C–H) insertion. Empirical studies are underway to clarify the significance of the vinyl substituent, perhaps as a means to uncover a complementary approach to this equally valuable class of chiral, α -substituted carbonyls.^{5c}

Given that a styrenyl 1,2-C–C bond shift precedes the formation of **24**, an analogous C–H bond migration in the Sc-complexed diazonium betaine could account for the predominance of ketone products (Scheme 1, path a).

Scheme 1. Possible Mechanisms for Net Insertion of Diazoalkyl Carbon Atoms into Aldehyde C–H Bonds under Sc(III) Catalysis



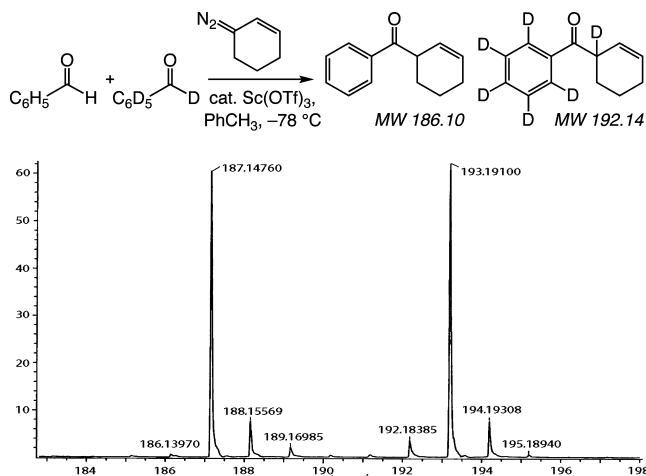
Appropriate control experiments have ruled out a pathway involving S_N2 closure to the epoxide and subsequent rearrangement.⁸ Nonetheless, a third plausible mechanism would invoke intermolecular E2 elimination of N_2 to give an enol intermediate followed by tautomerization (path b).

To distinguish between these two possibilities, a simple double-labeling experiment was performed (Scheme 2). Sc-catalyzed reaction of a 1:1 mixture of benzaldehyde and perdeuteriobenzaldehyde with 3-diazocyclohexene gives only the products of intramolecular C–H transfer according to high-resolution mass spectral analysis (ESI⁺). Though detectable in the scheme, peaks corresponding to H/D crossover occur at levels consistent with natural abundance and the starting enrichment for d_6 -PhCHO (97%). This mechanistic outcome is certainly desirable in the context of asymmetric catalysis of carbon insertion with aldehydes.

(7) Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem., Int. Ed.* **2008**, 47, 8933–8936.

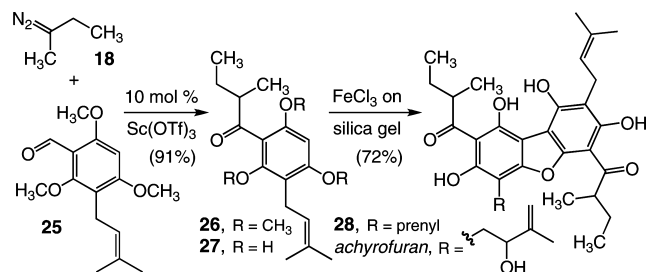
(8) Exposure of either *cis*- or *trans*-stilbene oxide to 10 mol % Sc(OTf)₃ in toluene at -78°C cleanly gives diphenylacetaldehyde upon warming. Epoxide rearrangement to aldehydes and ketones has been reported with the hydrates of erbium and cerium triflate: Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Sindona, G.; Tagarelli, A. *Synlett* **2004**, 2633–2635.

Scheme 2. Evidence for Intramolecular C–H Migration Pathway



As a test of the utility of catalytic carbon insertion with a complex aldehyde, we are targeting achyrofurane (Scheme 3), a potent antihyperglycemic recently found in extracts of *Achyrocline satureioides*.⁹ When administered orally to *db/db* mice at 20 mg/kg q.d., achyrofurane lowered blood glucose levels well below those in a control population exposed to metformin (dosed at 250 mg/kg q.d.), a drug

Scheme 3. A Concise Biomimetic Synthesis of “Pre-achyrofurane”



currently in clinical use to treat humans for type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM).¹⁰ The Supporting Information includes details for (1) a gram-scale synthesis of **26** from 2-diazobutane (**18**) and *m*-prenyl-trimethoxybenzaldehyde **25** in 91% yield and (2) biomimetic oxidative dimerization of the free triphenol **27** with regioselective dibenzofuran ring closure to give “pre-achyrofurane” (**28**). Noteworthy is that the relative and absolute configuration of the antidiabetic is still unknown. Although selectivity issues for the required oxidative transposition at the southern prenyl domain

(9) Carney, J. R.; Krenisky, J. M.; Williamson, R. T.; Luo, J. J. *Nat. Prod.* **2002**, 65, 203–205.

(10) For general commentary on new leads in the treatment of diabetes, see: Jarvis, L. M. *Chem. Eng. News* **2008**, 86, 34–36.

promise to be formidable challenges, stereodivergence could be important in elucidating the correct structure of the natural product. These and related experiments pertinent to enantioselective carbon insertion¹¹ are underway in our laboratory.

Acknowledgment. The ACS Petroleum Research Fund (no. 5001009) and Boston College are funding this

(11) Alternative means to formally achieve carbon insertion: Katritsky, A. R.; Toader, D.; Linghong, X. *J. Org. Chem.* **1996**, *61*, 7571–7577.

research. We thank our colleague Evan Kantrowitz (Boston College) for calling our attention to the bioactive target achyrofuran. Mass spectrometry instrumentation at B. C. is supported by funding from the NSF (no. DBI-0619576).

Supporting Information Available: Characterization data and full experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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