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An Enantioselective Synthesis of 2-Aryl Cycloalkanones by Sc-Catalyzed Carbon Insertion

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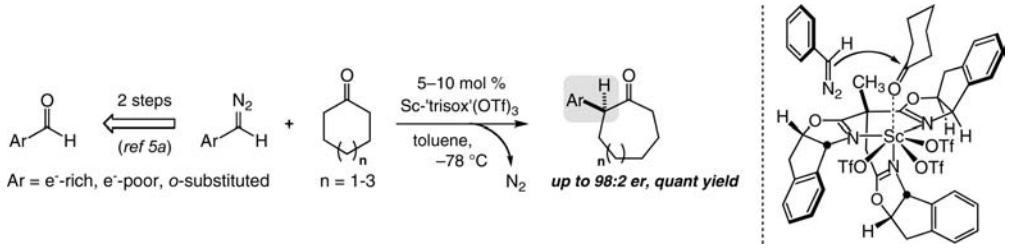
ABSTRACT



Current methods for asymmetric α-arylation require blocking groups to prevent reaction at the α′-carbon, basic conditions that promote racemization, or multistep synthesis. This work records the first catalytic enantioselective examples of the diazoalkane-carbonyl homologation reaction. Medium ring 2-aryl ketones are prepared in one step in up to 98:2 er and 99% yield from the unsubstituted lower homologue by Sc-catalyzed aryldiazomethyl insertion with simple bis- and tris(oxazoline) ligands.

One of the most routine C−C bond constructions in synthesis is the α-alkylation of ketone enolates. Both auxiliary-based[1] and catalytic enantioselective versions[2] of this process are well-known. Still, deficiencies in reaction scope and generality remain, and the widespread utility of α-substituted carbonyls as pharmaceutical and natural product building blocks justifies the development of complementary methods. We have been drawn to the simplicity that accompanies the direct insertion of carbon into the alpha C−C (or C−H) bond of ketones and aldehydes, an event enabled by the donor−acceptor properties of diazoalkanes.[3] Little preparative value[4] has come from noncarbonyl-stabilized, substituted diazomethanes because, until recently, practical methods[5] for their synthesis did not exist. Their service as carbon nucleophiles has also been impeded by the fact that the stoichiometric promoters[6] of carbonyl addition become ineffective (alcohols) or give competitive decomposition (BF_3 and $AlCl_3$) when the diazoalkyl carbon is sterically hindered and less reactive.[3] After discovering that inexpensive Sc^{3+} salts catalyze the diazoalkane-carbonyl homologation reaction, we reported new methods[7] for preparing α-substituted cyclic (***i***) and acyclic (***ii***) ketones (Scheme 1). More recently, we began

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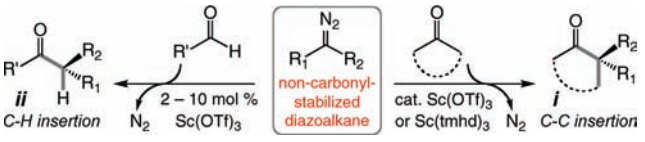
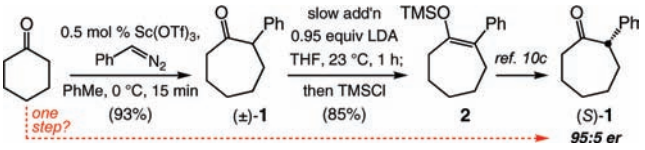
Scheme 1. Varied Strategies for Alicyclic and Linear Ketone Synthesis by Catalytic Diazoalkane−Carbonyl Homologation



screening chiral ligands for enantioselective reactions. Asymmetric strategies[8] for Roskamp β-keto ester synthesis with α-alkyl diazoacetates have been reported, including a catalytic one[8b] based on the use of chiral *N*,*N*′-dioxide−Sc^{3+} salts. Herein, we report a direct approach to nonracemic 2-aryl cycloalkanones with bis- and tris(oxazoline) ligands.

Tertiary α-aryl ketones are an ideal proving ground for the method, since they are not accessible by cross-coupling strategies[9] due to facile racemization. The only workable approach to these synthons is based on enantioselective protonation.[10] In advance of our experiments, we prepared authentic optically active 2-phenyl cycloheptanone (**1**) by the three-step sequence shown in Scheme 2 to test its configurational stability under the reaction conditions. After catalytic benzyl insertion with cyclohexanone and 0.5 mol % $Sc(OTf)_3$ to access racemic **1** and careful trimethylsilylation of its thermodynamic enolate (→**2**), a face-selective protonation with BINAP•AgF as the catalyst gave (*S*)-**1** in 95:5 er.[10c] Upon exposure of this material to phenyldiazomethane, $Sc(OTf)_3$, or a combination of the two (toluene, 0 °C, 6 h) no loss in enantiopurity was observed (95:5 er by chiral SFC).

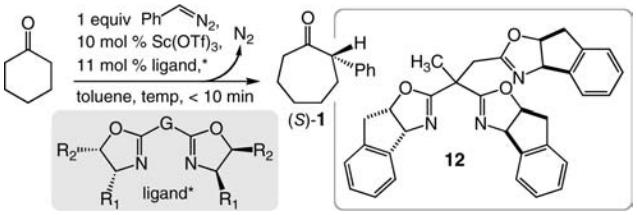
Scheme 2. Efficient Benzyl Insertion with Cyclohexanone and Its Potential to Streamline Access to Homochiral Aryl Ketones



These results support the mildness of our strategy and underscore the benefits of eliminating the arylation and enolsilylation steps that must precede protonation.

Among the multidentate ligands for catalytic asymmetric synthesis with the lanthanides,[11] those based on pyridylbis(oxazoline) are the most well characterized.[12]

Table 1. Box Ligand Screen for Bn Insertion in Cyclohexanone[a]



entry	T (°C)	ligand	linker (G)	R_1	R_2	er[b]
1	−60	**3**	2,6-pyridyl	Ph	H	57:43
2	−78	**4**	CH_2	Bn	H	55:45
3	−78	**5**	CH_2	Ph	Ph	75:25
4	−78	**6**	$C(CH_3)_2$	Ph	Ph	84:16
5	−78	**7**	$C(CH_2)_2$	Ph	Ph	87:13
6	−78	**8**	$C(CH_3)_2$	Bn	H	91:9
7	−78	**9**	$C(CH_3)_2$	−indanyl−		91:9
8	+4	**8**	$C(CH_3)_2$	Bn	H	53:47
9	−78	**10**	$C(CH_3)$(Ph-ox)	Ph	H	93:7
10	−78	**11**	$C(CH_3)$[(Ph-ox)CH_2]	Ph	H	91:9
11	−78	**12**	$C(CH_3)$[(indanyl-ox)CH_2]	−indanyl−		95:5[c]

[a] 0.2 M toluene and 25 mol % THF as cosolvent; > 98% conv in each entry. [b] By chiral SFC analysis. [c] Without THF.

Our study continued with an evaluation of [Sc(*R*,*R*)-Ph-pybox](OTf)$_3$ as the catalyst for enantioselective homologation of cyclohexanone with phenyldiazomethane. As shown in entry 1 of Table 1, measurable stereoinduction is observed at −60 °C with the catalyst prepared from $Sc(OTf)_3$ in situ with a slight excess of the ligand. We therefore tested[13] other box derivatives, judging that the nature of the linker could affect the Lewis acidity of the trication and its proximity to the blocking groups. Bidentate ligands with a CH_2 spacer (**4**, entry 2) gave higher reactivity, allowing > 98% conversion in < 10 min at −78 °C. Ligand **5**, derived from a diphenyl amino alcohol, was particularly effective (entry 3). It was then observed that geminal substitution on the linking carbon was helpful (entry 4). High crystallinity in the tetraphenyl series facilitated the study of bite angle effects in the context of cycloalkyl linkers.[14] Bis(oxazolinyl)-cyclopropane **7** was superior to its 4-, 5-, and 6-C ring variants (entry 5, other data not included).[13] Reaction with **8**, containing a dimethyl linker and benzyl blocking groups, further improved the enantiomer ratio to 91:9 in a result curiously matched by the rigid hexacycle **9** (entries 6 and 7). Warming of the reaction mixture gave poor selectivity (entry 8), and a solvent screen showed that toluene was optimal. Premixing the substrate with catalyst was also critical for high

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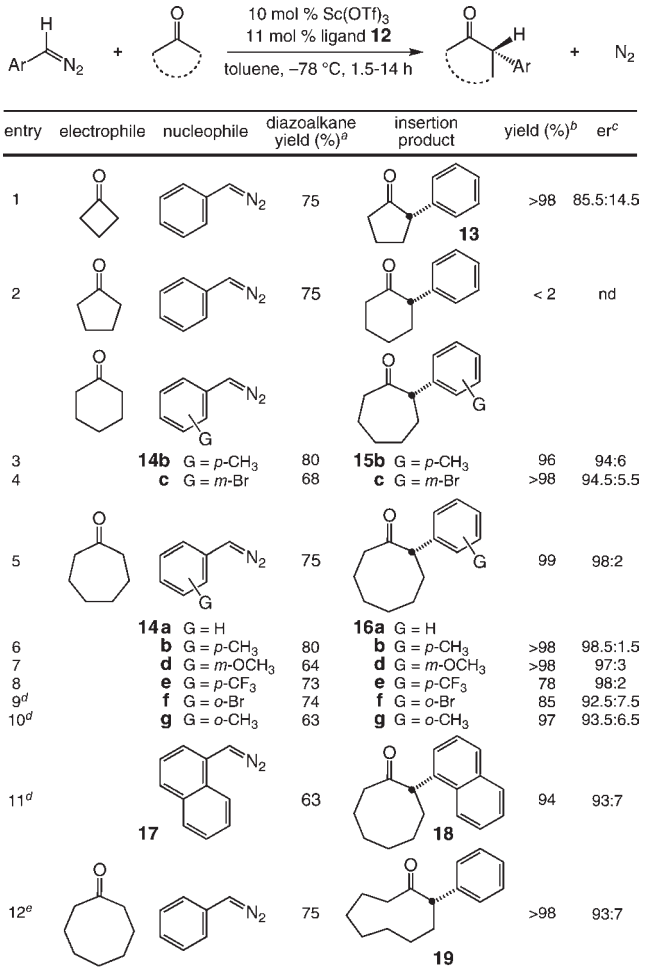
selectivity. At this point, it was fitting to consider polyvalency: adventitious moisture in the reagents lowered the selectivities, and the NMR spectra of several $Sc(OTf)_3$-ligand mixtures showed heterogeneity and line broadening consistent with complex coordination equilibria. Concerned that two ketones might be bound to Sc during turnover, we screened C_3-[15a,b] (**10**) and pseudo C_3-symmetric[15c,d] (**11**) tris(oxazolines) with the results seen in entries 9 and 10. A 95:5 er was observed for **12** (entry 11).

Table 2. Asymmetric Arylation by Diazoalkane Ring Expansion

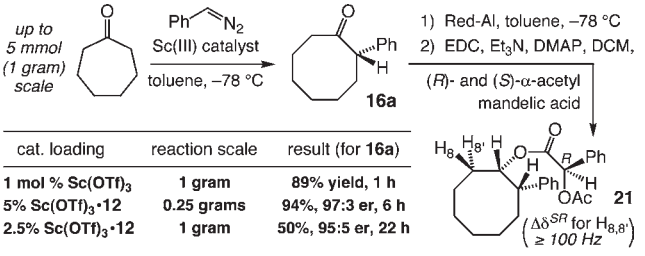


entry	electrophile	nucleophile	diazoalkane yield (%)[a]	insertion product	yield (%)[b]	er[c]
1			75	**13**	>98	85.5:14.5
2			75		< 2	nd
3		**14b** G = *p*-CH_3	80	**15b** G = *p*-CH_3	96	94:6
4		**c** G = *m*-Br	68	**c** G = *m*-Br	>98	94.5:5.5
5			75		99	98:2
		14a G = H		**16a** G = H		
6		**b** G = *p*-CH_3	80	**b** G = *p*-CH_3	>98	98.5:1.5
7		**d** G = *m*-OCH_3	64	**d** G = *m*-OCH_3	>98	97:3
8		**e** G = *p*-CF_3	73	**e** G = *p*-CF_3	78	98:2
9[d]		**f** G = *o*-Br	74	**f** G = *o*-Br	85	92.5:7.5
10[d]		**g** G = *o*-CH_3	63	**g** G = *o*-CH_3	97	93.5:6.5
11[d]		**17**	63	**18**	94	93:7
12[e]			75	**19**	>98	93:7

[a] Yield over two steps from the aldehyde[5a] based on ^{19}F NMR titration with *o*-$FC_6H_4CO_2H$. [b] After column chromatography. [c] By chiral SFC analysis. [d] With ligand **9**. [e] Run at −45 °C.

Initial findings on the scope of this process are compiled in Table 2. 2-Phenylcyclopentanone (**13**) can be acquired in >95% purity and 86:14 er by an aqueous wash of the reaction mixture and trituration to remove the ligand. Novel ligands are needed to improve the enantioselectivity of 4→5C ring homologations, but entry 1 is of value since the product racemizes easily on silica gel.[2j] As expected, reaction with cyclopentanone (entry 2) gives a complex mixture derived from overhomologation; here the monoinsertion product is more reactive than the starting material.[6] The remaining entries illustrate that a range of aryl diazomethanes apply to the asymmetric syntheses of seven-, eight-, and nine-membered rings in uniformly excellent yields. Alkyl and halogen groups on the nucleophile provide er's that are nearly identical to the 95:5 selectivity optimized for **1** (entries 3 and 4). Higher levels of asymmetric induction are observed for cycloheptanone (→**16a**, 98:2 er, entry 5). Entries 6−8 show that *p*-methyl, *m*-methoxy, and *p*-trifluoromethyl groups are easily tolerated. Use of more hindered *ortho*-substituted nucleophiles **14f** and **14g** results in diminished reactivity with ligand **12** at the cold temperatures needed to ensure high enantiocontrol. In these cases, however, the parent ligand **9** restores a rapid and smooth merger of the reactants presumably due to a less crowded Sc coordination sphere (→**16f** and **g**, 93:7 er, entries 9 and 10). The same trend is observed when 1-napthyldiazomethane (**17**) is used to prepare aryloctanone **18** (93:7 er, entry 11). Catalytic benzyl insertion with cyclooctanone is slower (14 h), but a 93:7 er for **19** can be achieved at −45 °C (entry 12).

Scheme 3. Gram-Scale Experiments with Low Catalyst Loadings



cat. loading	reaction scale	result (for **16a**)
1 mol % $Sc(OTf)_3$	**1 gram**	**89% yield, 1 h**
5% $Sc(OTf)_3$·12	**0.25 grams**	**94%, 97:3 er, 6 h**
2.5% $Sc(OTf)_3$·12	**1 gram**	**50%, 95:5 er, 22 h**

Results compiled in Scheme 3 confirm that the method is scalable and that lower catalyst loadings are acceptable. A rapid (< 1 h) and high-yielding racemic synthesis of **16a** is accomplished with 1 mol % $Sc(OTf)_3$ on a gram scale. Experiments with the chiral complex show that Sc^{3+} is less active and robust with a ligand present. Nonetheless, a 94% yield of **16a** in 97:3 er is possible with 5 mol % catalyst in just 6 h (1.25 mmol scale). A further drop in loading to 2.5 mol % still affords pure product in high er (95:5); in this case the reaction is incomplete after 1 d, but a 50% distilled yield of **16a** can be obtained on a 5 mmol scale after 22 h. Absolute stereochemical assignments (entries 1−4, Table 2) follow from optical rotation data reported for protonation methods.[10] Reduction of **16a** (3:1 dr, no stereomutation) gives *cis*-2-phenylcyclooctanol (**20**) and, upon esterification to the α-acetyl mandelates (**21**), an NMR-based proof of absolute configuration in the larger rings (entries 5−11).[13,16]

These data allow a tentative basis for stereochemical control to be set forth. As illustrated below in Scheme 4, enantioselective carbon insertion appears to derive from (1) the axial approach of the nucleophile with the diazoalkyl proton positioned over the cycloalkanone ring and the aryl group directed away from the chiral pocket established

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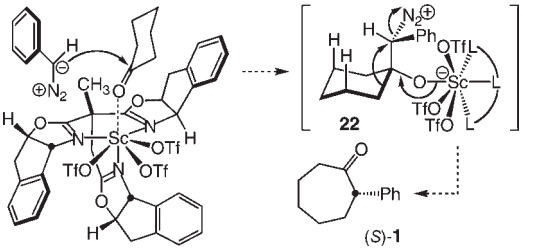
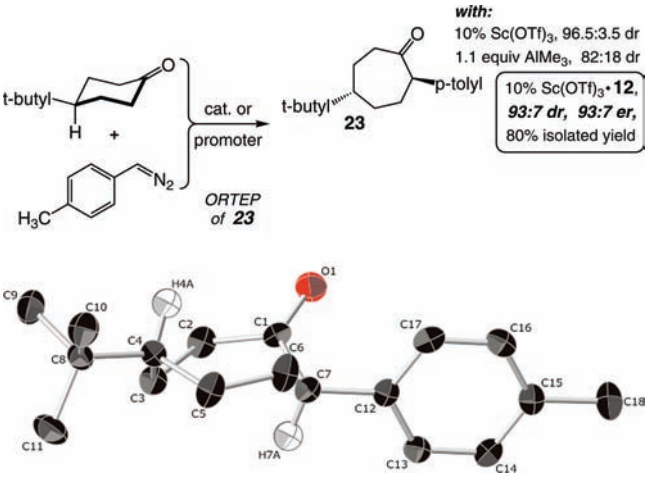
Scheme 4. Opening Mechanistic Model with Predictive Power



by the trisox ligand, (2) C−C bond formation to furnish diazonium Sc-alkoxide **22**, and (3) a least motion collapse of this intermediate by concerted 1,2-rearrangement and loss of dinitrogen. It deserves mention that a similar model based on *hexa*coordinate Sc^{3+} applies in the event that the third oxazoline unit is not bound or for those reactions that are most efficient with bis(oxazoline) **9** (entries 9−11, Table 2). To garner support for the proposed axial mode of diazoalkane-carbonyl addition, a singular example of enantio- and diastereoselective arylmethine insertion has been tested. The predicted outcome if betaine intermediate **22** were to possess a large equatorial substituent at the 4-position of the cyclohexanone would be a trans-disubstituted cycloheptanone.

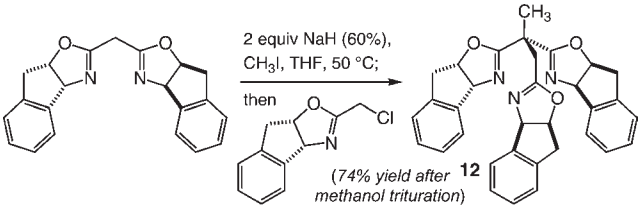
Scheme 5. Diastereo- and Enantiocontrol with a Prochiral Center



As depicted in Scheme 5, treating a solution of 4-*tert*-butyl cyclohexanone and 10 mol % $Sc(OTf)_3$ (toluene, −78 °C) with *p*-tolyldiazomethane results in the stereoselective formation of **23**, whose 2,5-relative configuration was confirmed by X-ray crystallography on the purified major diastereomer. The reaction dr is lower under conditions promoted by trimethylaluminum, yet consistent with a precedent set by Yamamoto using MAD and diazoethane;[6] the trans isomer is still preferred. Asymmetric catalysis of the merger under the standard conditions with ligand **12** provides 80% of pure **23** in 93:7 er. Since MAD was first applied to the synthesis of equatorial alcohols, enforcing an axial approach of carbon nucleophiles during carbonyl alkylation,[17] the results seem consistent with the rationale provided in Scheme 4.[18]

Currently, the scope of this transformation does not extend to heteroaromatic diazoalkanes. Homologation of cyclohexanone with various diazomethyl furans and thiophenes is successful but not highly enantioselective, perhaps owing to coordination by O (and S) and disruption of an optimum geometry within the trication. However, our results represent the first synthesis of α-arylcyclooctanones and -nonanones in enantioenriched form and complement the existing multistep approaches to small ring tertiary aryl ketones.[2j,10] Some *Goniothalamus* (Annonaceae family) plants produce metabolites[19] with eight-membered styryl ζ-lactone rings that are cytotoxic and inhibit mitochondrial complex I (NADH/ubiquinone oxidoreductase). Such structures could be approached by teaming catalytic asymmetric benzyl insertion with a regioselective Baeyer−Villiger reaction.[20] Additional studies with aliphatic and disubstituted diazoalkanes (to afford α-quaternary carbons) are underway in this laboratory. Our one-pot approach to tris(oxazolines) such as **12** (Scheme 6) starts from a simple box ligand and can aid in our efforts to broaden the scope.

Scheme 6. An Improved Synthesis of Tris(oxazoline) Ligands



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Supporting Information Available. Procedural details, characterization, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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