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Catalytic Asymmetric Formal Insertion of Aryldiazoalkanes into the C−H Bond of Aldehydes: Synthesis of Enantioenriched Acyclic α-Tertiary Aryl Ketones

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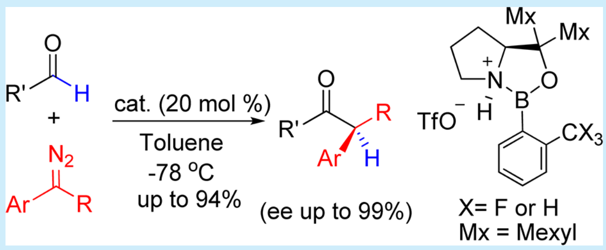
Supporting Information

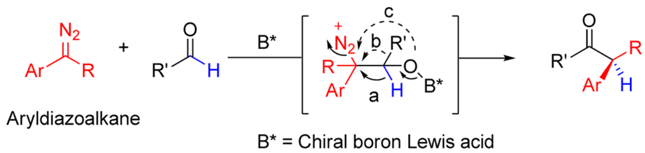
ABSTRACT: A novel, catalytic enantioselective route to synthesize a variety of α-tertiary aryl ketones via a boron Lewis acid promoted formal insertion of aryldiazoalkane into the C−H bond of both aromatic and aliphatic aldehydes is described. In the presence of chiral (*S*)-oxazaborolidinium ion catalyst **1**, the reaction proceeded in good yields (up to 94%) with excellent enantioselectivities (up to 99% ee).



α-Aryl ketones and cycloalkanones are useful building blocks for the synthesis of natural products and pharmaceuticals.[1] Due to their ubiquity and utility, the development of transition-metal-catalyzed α-arylation reactions has attracted considerable attention in past decades.[2] Despite successful pioneering studies on enantioselective α-arylation to generate chiral quaternary carbon centers,[2,3] catalytic enantioselective construction of α-tertiary aryl alkanones[4] and cycloalkanones[5] has only recently been realized, presumably due to racemization of the product in related transition-metal-catalyzed α-arylation methods. For specific examples that address preparative access to more elusive acyclic α-tertiary aryl ketones, Fu and co-workers reported nickel catalyzed asymmetric Kumada and Negishi cross-coupling reactions to afford enantioenriched α-tertiary aryl ketones.[4a,b] Reisman and co-workers developed a nickel−bis(oxazoline)-catalyzed reductive acyl cross-coupling reaction in the presence of manganese as a stoichiometric reductant.[4c] In a complementary approach, the Toste group developed a gold-catalyzed enantioselective protonation of enolsilane.[4d] However, limited substrate scope and low yields from homocoupling have necessitated the development of new catalytic enantioselective methods.

The Roskamp reaction,[6] a Lewis acid catalyzed homologation of aldehydes using α-diazoester, has been a popular and useful synthetic method to construct β-ketoesters, and catalytic asymmetric methods have recently been reported by both the Feng laboratory[7a] and our group.[7b] Strategically, we envisioned that the use of an aryldiazoalkane[8] instead of an α-diazoester could provide a transition-metal-free coupling[9] approach to prepare enantioenriched acyclic α-tertiary aryl ketones (Scheme 1). To the best of our knowledge, the use of noncarbonyl-stablilized[10] aryldiazoalkanes for the synthesis of acyclic chiral ketones is without precedent.[5,11] Herein, we describe the successful development of the first catalytic enantioselective formal C−H insertion reaction of aryldiazoalkanes to afford highly optically active α-tertiary aryl ketones.

Scheme 1. Lewis Acid Catalyzed Formal Insertion of Aryldiazoalkane into the C−H Bond of Aldehyde



Initially, an asymmetric formal C−H insertion reaction between 1-phenyldiazoethane and benzaldehyde was examined in the presence of 20 mol % of oxazaborolidinium ion **1a** activated by triflic imide (Table 1, entry 1). When the reaction was carried out at −78 °C in CH_2Cl_2, the desired optically active α-tertiary aryl ketone **2a** was obtained as the major product via a selective 1,2-hydride shift (Scheme 1, path a). A minor phenyl migration product **3a** was also isolated in 24% yield (Scheme 1, path b). Use of the nonpolar solvent toluene led to an increased ratio of the desired product in 69% yield and 85% ee (Table 1, entry 2). We then screened the catalyst structure and found that the catalyst system with a 2,4-dimethylphenyl Ar substituent and 2-(trifluoromethyl)-phenyl R substituent, activated by triflic acid, gave the best result (Table 1, entries 3−6). The yield of **2a** improved to 86%, in 95% ee with a **2a**/**3a** ratio of 7:1 (Table 1, entry 5).[12]

With optimized reaction conditions for the catalytic asymmetric formal C−H insertion reaction in hand, we evaluated this methodology with a range of substituted aromatic aldehydes (Table 2). Regardless of the electronic properties of substituents

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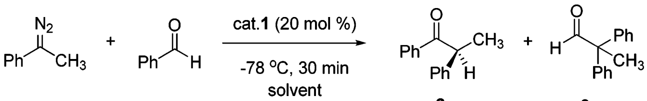
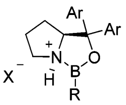
Table 1. Optimization of the Asymmetric Formal insertion of 1-Phenyldiazoethane into the C−H Bond of Benzaldehyde[a]



2a 3a



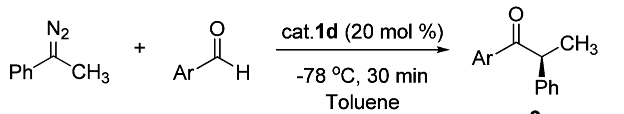
1a, Ar = Phenyl, R = Phenyl, X = Tf_2N
1b, Ar = 3,5-Dimethylphenyl, R = Phenyl, X = Tf_2N
1c, Ar = 3,5-Dimethylphenyl, R = 2-(Trifluoromethyl)phenyl, X = Tf_2N
1d, Ar = 3,5-Dimethylphenyl, R = 2-(Trifluoromethyl)phenyl, X = TfO
1e, Ar = 3,5-Dimethylphenyl, R = *o*-Tolyl, X = TfO

Catalyst

entry	solvent	cat.	2a/3a[b]	yield[c] (%)	ee[d] (%)
1	CH_2Cl_2	**1a**	3:1	60	70
2	toluene	**1a**	4:1	69	85
3	toluene	**1b**	6:1	85	93
4	toluene	**1c**	4:1	73	97
5	toluene	**1d**	7:1	86	95
6	toluene	**1e**	5:1	82	84

[a]The reaction of 1-phenyldiazoethane (0.35 mmol) with benzaldehyde (0.23 mmol) was performed in the presence of **1** (20 mol %) in 1.0 mL of solvent at −78 °C for 30 min. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yield of **2a**. [d]The ee of **2a** was determined by chiral HPLC.

Table 2. Asymmetric Formal Insertion of 1-Phenyldiazoethane into the C−H Bond of Aromatic Aldehydes[a]



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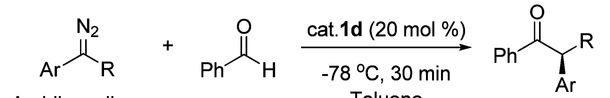
entry	2	Ar	yield[b] (%)	ee[c] (%)
1	**2a**	Ph	86	95
2	**2b**	4-MePh	85	93
3	**2c**	4-MeOPh	80	95
4[d]	**2d**	4-BrPh	74	95
5[e]	**2e**	4-CF_3Ph	75	95
6[d]	**2f**	4-CNPh	74	99
7[e]	**2g**	4-NO_2Ph	76	94
8	**2h**	2-FPh	40	96
9	**2i**	2-thienyl	83	96
10	**2j**	2-furyl	83	90
11[e]	**2k**	2-Naph	73	97

[a]The reaction of 1-phenyldiazoethane (0.35 mmol) with aromatic aldehydes (0.23 mmol) was performed in the presence of **1d** (20 mol %), in 1.0 mL of solvent at −78 °C for 30 min. [b]Isolated yield of **2**. [c]The ee of **2** was determined by chiral HPLC. [d]The reaction was performed at −50 °C. [e]The reaction was performed at −30 °C.

Table 3. Asymmetric Formal Insertion of Various Aryldiazoalkanes into the C−H Bond of Benzaldehyde[a]



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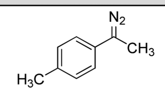
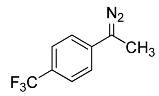
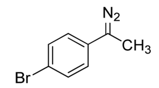
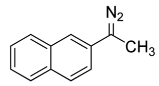
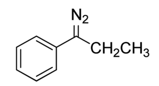
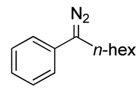
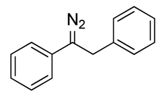
entry	2	aryldiazoalkane	yield (%)[b]	ee (%)[c]
1	**2l**		80	97
2	**2m**		88	87
3	**2n**		86	91
4	**2o**		82	97
5	**2p**		78	95
6	**2q**		83	92
7	**2r**		75	92

[a]The reaction of aryldiazoalkane (0.35 mmol) with benzaldehydes (0.23 mmol) was performed in the presence of **1d** (20 mol %) in 1.0 mL of solvent at −78 °C for 30 min. [b]Isolated yield of **2**. [c]The ee of **2** was determined by chiral HPLC.

on the aromatic aldehyde, highly optically active *α*-tertiary aryl ketones **2** were obtained. Interestingly, *o*-fluorobenzaldehyde gave the desired product **2** in lower yield because of competing epoxide formation (Table 2, entry 8) via an undesired Darzens reaction (Scheme 1, path c).[13]

To further investigate the substrate scope of the present catalytic system, we performed the catalytic asymmetric C−H insertion reaction with a range of aryldiazoalkanes and benzaldehyde. As summarized in Table 3, the electronic properties of the aryldiazoalkane obviously affected the yield and enantioselectivity of the product (Table 3, entries 1−3). Electron-rich aryldiazoalkane substrate gave enhanced enantioselectivity but in lower yield (Table 3, entry 1). Conversely, electron-deficient substrates caused a modest reduction of the ee value but produced higher yields of products (Table 3, entries 2 and 3). More sterically bulky naphthyl and ethyl as well as longer normal hexyl- and benzyl-substituted aryldiazoalkanes reacted well with benzaldehyde to provide the corresponding *α*-tertiary aryl ketones **2** in good to high yields and high enantioselectivities (Table 3, entries 4−7). However, reactions of secondary alkyl substrates of the aryldiazoalkane were unfruitful.

Encouraged by the good results exhibited in Table 3, we applied this catalytic C−H insertion methodology to reactions of a range of aryldiazoalkanes and aliphatic aldehydes. However, the best chiral catalyst, **1d**, for aromatic aldehydes was not the optimal catalyst for aliphatic aldehydes. Catalyst **1e**, bearing an *o*-tolyl group on boron, was found to be more suitable for generating higher yields and enantioselectivities (Table 4, entries 1 and 2). As summarized in Table 4, propionaldehyde, long-chain heptaldehyde, as well as the more sterically hindered isopropyl and cyclohexyl carboxaldehyde successfully reacted with 1-phenyldiazoethane to provide the corresponding *α*-tertiary aryl ketones in high yields and high to excellent enantioselectivities (Table 4, entries 2−5). However, sterically bulky pivaldehyde did not react with 1-phenyldiazoethane at all (Table 4, entry 6). This catalytic system was also successfully applied to reactions of a range of aryldiazoalkanes with simple primary and secondary

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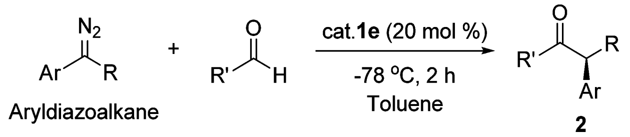
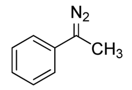
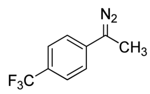
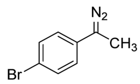
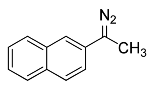
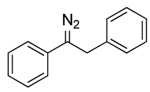
Table 4. Asymmetric Formal Insertion of Various Aryldiazoalkanes into the C−H Bond of Aliphatic Aldehydes[a]



entry	2	aryldiazoalkane	R'	yield (%)[b]	ee (%)[c]
1[d]	**2s**		Et	64	91
2	**2s**		Et	78	93
3	**2t**		*n*-hex	83	93
4	**2u**		*i*-Pr	94	98
5	**2v**		Cy	90	99
6[e]	**2w**		*t*-Bu	N.R	-
7	**2x**		Et	72	90
8	**2y**		*i*-Pr	72	97
9	**2z**		Et	80	92
10	**2za**		*i*-Pr	88	96
11	**2zb**		Et	67	98
12	**2zc**		*i*-Pr	84	98
13[f]	**2zd**		Et	55	95
14	**2ze**		*i*-Pr	68	96

[a]The reaction of aryldiazoalkane (0.35 mmol) with aliphatic aldehydes (0.23 mmol) was performed in the presence of **1e** (20 mol %), in 5.0 mL of solvent at −78 °C for 2 h. [b]Isolated yield of **2**. [c]The ee of **2** was determined by chiral HPLC. [d]The reaction was performed at −78 °C catalyzed by **1d**. [e]The reaction was performed at 0 °C. [f]1,2-alkyl shift, *α*-quaternary aldehyde **3zd** was isolated in 44% yield. Cy = cyclohexyl.

aliphatic aldehydes to provide the corresponding *α*-tertiary aryl ketones in good to high yields and excellent enantioselectivities (Table 4, entries 7−12 and 14).

The observed stereochemistry for the asymmetric formal C−H insertion reaction using oxazaborolidinium ion catalyst **1d** or **1e** can be rationalized using the transition-state model shown in Figure 1. The mode of coordination of aldehyde to **1d** and **1e** is the same as has been previously observed in enantioselective cyanosilylation,[14a] 1,3-dipolar cycloaddition,[14b,d] cyclopropanation,[14c] and Roskamp reaction.[7b] In the pre-transition-state assembly **4**, shown in Figure 1, the aldehyde group is situated above the mexyl group, which effectively shields the re face

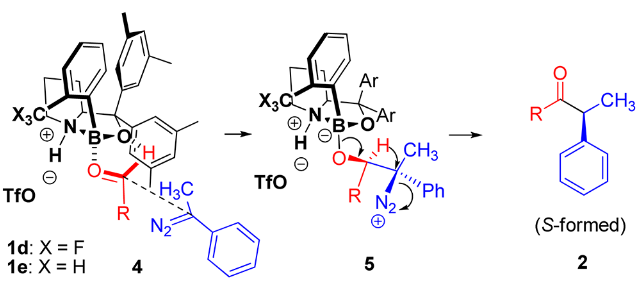
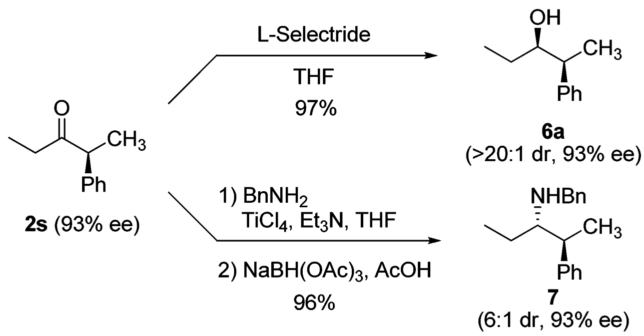


Figure 1. Transition-state model for the asymmetric formal C−H insertion of 1-phenyldiazoethane into aldehyde catalyzed by **1d** or **1e**.

(back) from attack by the aryldiazoalkane. Due to the steric interaction between the boron aryl substituent of the catalyst and the aryldiazoalkane phenyl group, the arydiazoalkane approaches the aldehyde for nucleophilic addition with the phenyl group situated away from the aldehyde group. Additionally, in the case of aromatic aldehydes (R = aryl, Figure 1), a possible *π*−*π* interaction between the aryl ring of the aromatic aldehyde with the aryldiazoalkane aryl group holds the two aryl rings together.[7d,15] Nucleophilic addition of the aryldiazoalkane from the si face (front) of the aldehyde leads to intermediate **5**. Chemoselective 1,2-hydride shift with loss of nitrogen provides the *α*-tertiary aryl ketone *S*-**2** as the major enantiomer. Comparison of the optical rotation data with literature values confirmed the absolute (*S*) stereochemistry of a representative aliphatic and aromatic substituted products [**2a**: $[\alpha]_D^{25} = +199$ ($CHCl_3$, *c* = 0.90; 95% ee); lit.[4b] $[\alpha]_D^{21} = +175$ ($CHCl_3$, *c* = 1.00; 92% ee), **2s**: $[\alpha]_D^{25} = +277$ ($CHCl_3$, *c* = 0.25; 93% ee); *ent*-**2s**: lit.[4c] $[\alpha]_D^{25} = -225.9$ ($CHCl_3$, *c* = 0.57; 91% ee)].[16]

Further chemical transformations of the resulting optically active *α*-tertiary aryl ketone are illustrated in Scheme 2.

Scheme 2. Functionalization of *α*-Tertiary Aryl Ketone



Reduction of **2s** with L-Selectride[17] led to the highly optically enriched secondary alcohol **6a**.[18] Additionally, reductive amination[4b,19] of **2s** with sodium triacetoxyborohydride gave secondary amine **7** with retention of ee.[20]

In summary, we have developed the first catalytic asymmetric formal insertion of aryldiazoalkanes into the C−H bond of both aromatic and aliphatic aldehydes. This mild and chemoselective transition-metal-free coupling reaction provides access to a variety of *α*-tertiary aryl ketones in good yields and high to excellent enantioselectivities. In two cases, the absolute configuration of the major product was the same as that predicted by the transition-state model in Figure 1. The resulting *α*-tertiary aryl ketones can easily be converted into enantioenriched secondary alcohol and amine without loss of optical purity. Additional applications of this catalytic asymmetric transformation and extension of the substrate scope are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02370.

Experimental procedures and full analytical data (PDF)

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Notes

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