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Storable and Air-Stable Zirconium Complex-Catalyzed Highly Enantioselective Darzens Reaction of Diazoacetamide with Aldehydes

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Abstract: An asymmetric Darzens reaction of aldehydes with diazo-*N,N*-dimethylacetamide (**3**) catalyzd by an air-stable and storable chiral zirconium Lewis acid catalyst, which is formed from 3,3′-diiodobinaphthol and tetrabutoxyzirconium, gives solely the *cis*-glycidic amides in high yields with excellent enantioselectivity (up to 97% yield, >99% *ee*).

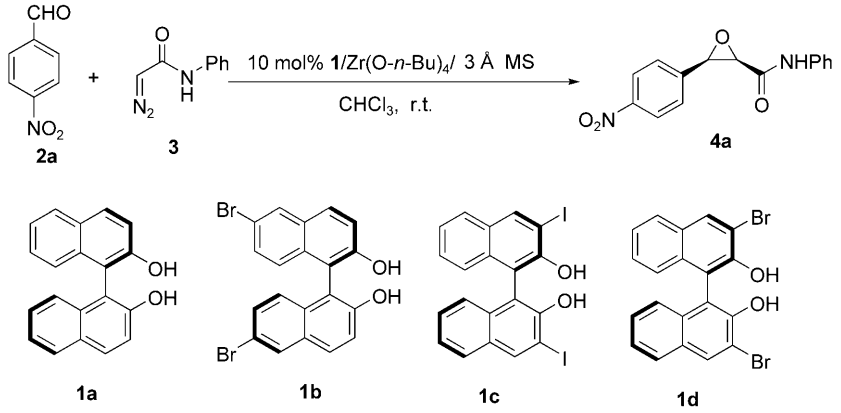
Keywords: asymmetric catalysis; Darzens reaction; epoxides; *cis*-glycidic amides; zirconium Lewis acids

Optically pure epoxides represent one of the most important types of chiral intermediates with a broad array of applications in organic synthesis.[1] In particular, glycidic esters and amides have attracted much interest as chiral building blocks in the synthesis of some key chiral intermediates to construct pharmaceutically relevant molecules because they contain the additional ester and amide functional groups to thereby facilitate transformations with a great degree of regio- and stereocontrol.[2] The most common approach to access these molecules in enantiomerically enriched form is the asymmetric epoxidation of the corresponding α,β-unsaturated carbonyl compound with the diastereochemistry essentially being dependent on the configuration of the carbon-carbon double bond.[3,4] The Darzens reaction has been known for over 100 years and has been recognized as one of the most powerful methods to produce α,β-epoxy carbonyl and related compounds.[5] Although numerous efforts have been dedicated to the discovery of an enantioselective Darzens reaction, very few successful examples of the catalytic asymmetric variants have been reported with synthetically useful stereoselectivity.[6] Very recently, we found a chiral titanium(IV) Lewis acid-catalyzed Darzens reaction of diazo-*N,N*-dimethylacetamide (**3**) with a wide range of aldehydes, providing *cis*-epoxides in high yields with excellent enantioselectivity.[7] Although promising, titanium-based chiral Lewis acids are usually sensitive to air and moisture and thus have to be prepared *in situ* under strictly anhydrous and inert conditions. Consequently, a more storable and air-stable catalyst system for the asymmetric Darzens reaction would provide promise for the practical organic synthesis of epoxy carbonyls and amides in high enantiomeric purity.

Kobayashi and co-workers have continuously documented that the chiral zirconium complex of binaphthol combined with molecular sieves has been an effective catalyst for many transformations[8] including Mannich-type reaction,[9] aldol reaction,[10] Strecker reaction,[11] cycloaddition reaction,[12] aza Diels–Alder reaction,[13] allylation of imines,[14] and epoxidation reaction.[15] These successes and the storable and air-stable features of zirconium complexes prompted us to develop a highly enantioselective Darzens reaction by using them as chiral catalysts.

Initially, we explored the Darzens reaction of diazo-*N,N*-dimethylacetamide (**3**) with 4-nitrobenzaldehyde (**2a**) in $CHCl_3$ at room temperature by using 10 mol% of the zirconium complex of (*R*)-binol combined with 3 Å molecular sieves, which was prepared following the procedure reported by Kobayashi and co-workers.[8,9] Encouragingly, the reaction proceeded smoothly to generate *cis*-glycidic amide (**4a**) in 57% yield with 71% *ee* (Table 1, entry 1). It is worth noting that this reaction exhibited excellent diastereoselectivity and the *trans*-diastereomer was not detectable by ^1H NMR analysis of the crude product. Interestingly, studies on the correlation between the binaphthol-

Table 1. Effect of chiral ligand on Darzens reaction of 4-nitrobenzaldehyde with diazo-*N,N*-dimethylacetamide.[a]



Entry	Ligand	Ligand/Zr	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	2:1	3	57	71 (*S,S*)
2	**1b**	2:1	3	50	59 (*S,S*)
3	**1c**	2:1	1	94	97 (*R,R*)
4	**1c**	2:1	1	88	96 (*R,R*)[d]
5	**1d**	2:1	1	92	95 (*R,R*)
6	**1c**	1:1	1	95	94 (*R,R*)
7	**1c**	1:2	1	95	91 (*R,R*)

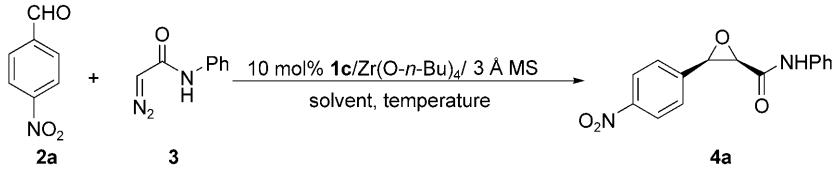
[a] The reaction was carried out on a 0.1 mmol scale in chloroform (1 mL) and the ratio of **2/3** was 1.2/1.
[b] Isolated yield.
[c] The *ee* was determined by chiral HPLC and the absolute configuration of the product was assigned by comparison of the optical rotation with that reported in the literature.[7]
[d] The reaction was conducted in the absence of 3 Å MS.

derived ligands **1b–1d** and the reaction performance revealed that 3,3′-substituents have considerable impact on the stereochemistry. In comparison with reactions using binaphthol and its 6,6′-substituted derivatives that preferred the (*S,S*)-epoxide, the introduction of 3,3′-substituents to the BINOL not only favored the generation of the opposite enantiomer but also provided an even faster reaction and higher enantiomeric excesses (Table 1, entries 2–5). The most optimal ligand turned out to be 3,3′-diiodobinaphthol (**1c**) in terms of the stereochemical outcome, which in combination with tetrabutoxyzirconium, delivered 94% yield and 97% *ee* to (*R,R*)-glycidic amide (**4a**) (Table 1, entry 3). Notably, we reported previously that the titanium complex of (*R*)-binaphthol also gave high yields and excellent enantioselectivity, but favored the formation of (*S,S*)-**4a**.[7] Thus the current protocol provided an important alternative complementary to the chiral titanium-catalyzed variant in addition to the advantages associated with the storable and air-stable characteristics. The absence of 3 Å molecular sieves led to a lower yield but with maintained *ee* (entry 4). Additional studies on the stoichiometry of **1c** and tetrabutoxyzirconium found that tuning the ratio of **1c**/tetrabutoxyzirconium from 2/1 to 1/2 led to a slightly decreased enantioselectivity (entries 3, 6 and 7).

Screening of different solvents indicated that the yield and enantioselectivity are both dependent on the solvent (Table 2). Thus, halogenated solvents such as chloroform, dichloromethane, and 1,2-dichloroethane gave comparably higher yields and enantioselectivity than oxygenated solvents such as diethyl ether and tetrahydrofuran and non-polar solvents as exemplified by toluene (entries 1–6). A much slower reaction was observed in a protic solvent although the enantioselectivity remained moderate (entry 7). Interestingly, a polar solvent, acetonitrile, provided the highest yield and enantioselectivity (entry 8). Consequently, the investigation of the temperature effect on the reaction performance was carried out in acetonitrile and we found that conducting the reaction at room temperature resulted in the highest levels of enantioselectivity (entries 8–11).

We then explored the generality of the protocol for the aldehyde component under the optimal conditions (Table 3). Benzaldehyde derivatives bearing electron-withdrawing substituents at either the *ortho* or *para* positions provided *cis*-epoxides in high yields and with excellent enantioselectivity (96 to >99% *ee*, entries 1–7 and 17–19). It is worth noting that the current Darzens reaction offered higher yields and enantioselectivity for *meta*-substituted benzaldehdyes than the previous variant by using a titanium complex cata-

Table 2. Effect of solvent and temperature on the Darzens reaction.[a]



Entry	Solvent	Time [h]	Temperature [°C]	Yield [%][b]	*ee* [%][c]
1	$CHCl_3$	1	25	94	97
2	CH_2Cl_2	1	25	76	97
3	DCE	1	25	97	98
4	$PhCH_3$	10	25	77	81
5	Et_2O	10	25	70	87
6	THF	10	25	74	89
7	CH_3OH	24	25	45	79
8	CH_3CN	1	25	96	>99
9	CH_3CN	1	40	98	97
10	CH_3CN	2	10	96	98
11	CH_3CN	3	0	96	98

[a] The reaction was carried out on a 0.1 mmol scale in solvent (1 mL) and the ratio of **2**/**3** was 1.2/1.
[b] Isolated yield based on **3**.
[c] Determined by chiral HPLC.

lyst (entries 8 and 10–12).[7] Electronically rich benzaldehdyes also engaged in a clean Darzens reaction with higher enantioselectivity than the titanium complex-catalyzed similar reaction (entries 13–15). Interestingly, the heteroaromatic aldehydes could also be tolerated with high stereoselectivity, as exemplified by picolinaldehyde (entry 16). The extension of the reaction conditions to aliphatic aldehydes including linear and branched aliphatic aldehydes was highly successful, giving rise to glycidic amides with 96–98% *ee* (entries 20–24). Benzyloxyacetaldehyde was able to participate in the Darzens reaction in 64% yield and with 91% *ee*, both values being lower than those obtained by using the titanium complex of binaphthol (entry 25). Interestingly, a substrate with an unprotected OH group in the aldehyde was also able to participate in Darzens reaction, as exemplified by 3-hydroxybenzaldehyde, providing a *cis*-epoxide in 76% yield and with 97% *ee* (entry 26).

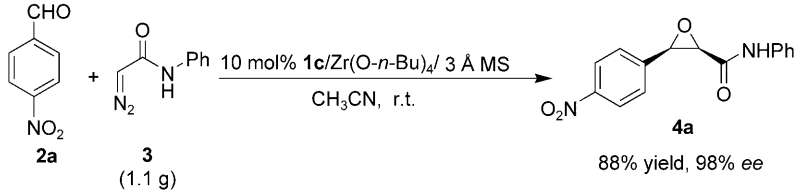
The current Darzens reaction could be scaled up to the gram-scale with maintained efficiency, albeit with a very subtle erosion of the stereoselectivity. For example, the reaction of **3** (1.1 g) with 4-nitrobenzaldehyde **2a** proceeded smoothly to give *cis*-epoxide **4a** in 88% yield and 98% *ee* (Scheme 1).

In summary, we have disclosed an asymmetric Darzens reaction of aldehydes with diazo-*N*,*N*-dimethylacetamide by using air-stable and storable chiral zirconium Lewis acid catalyst formed from 3,3′-diiodobinaphthol and tetrabutoxyzirconium, solely giving *cis*-glycidic amides with excellent enantioselectivity. The current protocol is easier to operate than the titanium-catalyzed variant and thus provides an important alternative to prepare epoxy amides with high enantiomeric purity. Further theoretical studies on transition states of reactions either by titanium[7] or zirconium complexes by DFT calculations to understand the stereochemistry are now underway and the related results will be reported in due course.

Experimental Section

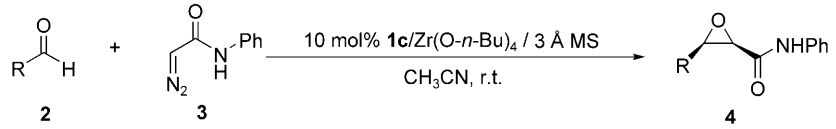
Preparation of (*R*)-3-I-ZrMs

The catalyst was prepared according to a literature procedure.[8] To a suspension of (*R*)-3,3′-diiodo-BINOL (107.5 mg, 0.2 mmol) in toluene (4 mL) was added $Zr(O\text{-}n\text{-}Bu)_4$



Scheme 1. Gram-scale synthesis of *cis*-epoxide **4a**.

Table 3. Enantioselective Darzens reaction of various aldehydes.[a]



Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	4-$NO_2C_6H_4$	**4a**	96	>99
2	Ph	**4b**	94	99
3	4-FC_6H_4	**4c**	96	99
4	4-$MeO_2CC_6H_4$	**4d**	92	97
5	4-ClC_6H_4	**4e**	81	96
6	4-BrC_6H_4	**4f**	82	>99
7	4-CNC_6H_4	**4g**	89	99
8	3-CNC_6H_4	**4h**	95	99
9	2-$NO_2C_6H_4$	**4i**	87	94
10	3-BrC_6H_4	**4j**	93	98
11	3-ClC_6H_4	**4k**	95	99
12	3-$CH_3OC_6H_4$	**4l**	94	>99
13	4-$CH_3C_6H_4$	**4m**	91	99
14	α-naphthyl	**4n**	97	>99
15	β-naphthyl	**4o**	95	>99
16	2-pyridinyl	**4p**	76	98
17	2-BrC_6H_4	**4q**	89	99
18	2-ClC_6H_4	**4r**	78	99
19	2-FC_6H_4	**4s**	88	99
20	CH_3CH_2	**4t**	83	97
21	$CH_3CH_2CH_2$	**4u**	97	97
22	$C_6H_5CH_2CH_2$	**4v**	82	98
23	$(CH_3)_2CHCH_2$	**4w**	73	95
24	*c*-C_6H_{11}	**4x**	93	98
25	$C_6H_5CH_2OCH_2$	**4y**	64	91
26	3-OHC_6H_4	**4z**	76	97[d]

[a] The reaction was carried out on a 0.1 mmol scale in CH_3CN (1 mL) at room temperature, and the ratio of **2**/**3** was 1.2/1.
[b] Isolated yields based on the **3**.
[c] The *ee* was determined by chiral HPLC and the absolute configuration of the product was assigned by comparison of the optical rotation with that reported in the literature.[7]
[d] The reaction was carried out at 40 °C.

(38.4 mg, 0.1 mmol) at room temperature, and the solution was stirred for 3 h at the same temperature. 3 Å MS (1.0 g) was added, and the mixture was stirred for 10 min. After removal of the solvents under reduced pressure, the resulting solid was dried at room temperature under the vacuum for 1 h, giving (*R*)-**3**-I-ZrMs, which was used directly.

General Procedure for the Asymmetric Darzens Reactions

To a suspension of (*R*)-**3**-I-ZrMs catalyst (0.01 mmol, 10 mol%) in CH_3CN was added an aldehyde (0.12 mmol) and diazo-*N*,*N*-dimethylacetamide (**3**) (0.1 mmol). The reaction mixture was stirred at 25 °C until the reaction was complete (monitored by TLC). Then the reaction mixture was filtered to remove molecular sieves, and the solid powder was washed with ethyl acetate (5.0 mL). After evaporation under reduced pressure, the residue was purified through flash column chromatography on silica gel (eluent: petroleum ether: ethyl acetate = 15:1–1:1) to yield pure products (**4a–4z**).

Supporting Information

Experimental details and characterization data of new compounds are given in the Supporting Information.

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