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New Electrophilic Addition of α-Diazoesters with Ketones for Enantioselective C−N Bond Formation

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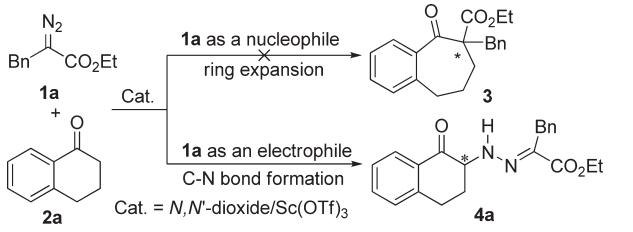
Supporting Information

ABSTRACT: α-Diazoesters were discovered to be good electrophiles in a catalytic asymmetric α-functionalization of ketones for the first time. This reaction also provided a direct and efficient method for C−N bond formation with excellent yields (up to 98%) and enantioselectivities (up to 99% ee) under mild conditions. The application of the electrophilicity of α-diazoesters opens up a novel way to access the diversity of diazo chemistry.

The chemistry of α-diazocarbonyl compounds has attracted great attention because of its extensive applications in organic chemistry since the first recorded synthesis of ethyl diazoacetate by Curtius in 1883.[1] Remarkably, α-diazocarbonyl compounds have been well-studied as metal carbene precursors,[2] 1,3-dipoles,[3] and nucleophiles.[4] Comparatively, the utility of the electrophilic capability of α-diazocarbonyl compounds has rarely been studied. One related reaction is the Japp−Klingemann reaction, in which aryldiazonium compounds are used as the electrophiles and are attacked by β-ketoesters under basic conditions to form arylhydrazone compounds.[5] Another direct nucleophilic addition to α-diazoesters using highly active organolithium reagents and Grignard reagents under rigorous conditions was recently reported by Takamura and co-workers.[6]

In our previous study of the chiral Lewis acid-catalyzed reaction between α-diazoesters and aromatic aldehydes, an efficient catalytic asymmetric Roskamp reaction was accomplished by using the nucleophilicity of α-diazoesters.[7] Continuous experiments were carried out to explore the reaction between α-diazoesters and ketones under similar reaction conditions. It was rationally expected that a ring-expansion product would be obtained from the initial nucleophilic addition of the α-diazoester to the C═O bond of the ketone.[8] To our great surprise, the unexpected alkylhydrazone compound **4a** was obtained from the reaction between 1-tetralone (**2a**) and α-benzyl-α-diazoacetate (**1a**), and no related ring-expansion product **3** was observed (Scheme 1). Herein we report this new reaction involving the electrophilic addition of α-diazoesters to α-alkyl ketones under mild reaction conditions. Meanwhile, a highly catalytic asymmetric α-hydrazonation of unactivated ketones to construct homochiral C−N bonds with exceptional enantioselectivities was accomplished. It is also a potential alternative approach to α-amination of ketones.[9]

Scheme 1. Observations from the Reaction between 1-Tetralone (2a) and α-Benzyl-α-diazoester (1a)



In the initial study, the reaction between **2a** and **1a** was performed in CH_2Cl_2 at 20 °C with a 10 mol % loading of a Lewis acid catalyst prepared in situ from a metal salt and the chiral *N*,*N*′-dioxide ligand **L1**.[10] Excellent enantioselectivity but a very low yield of the particular alkylhydrazone compound **4a** was obtained in the presence of the **L1**−$Sc(OTf)_3$ complex (Table 1, entry 1). Other metal sources, including $Y(OTf)_3$, $La(OTf)_3$, and $Sc(OiPr)_3$, were evaluated and failed to catalyze the reaction (entries 2−4). To improve the reactivity, it was envisioned that bases might be favorable toward the enolization of **2a**, thereby enhancing its nucleophilic capability. To our delight, when 10 mol % K_2CO_3 was added as a basic additive, the yield increased to 33% while the enantioselectivity was maintained (entry 5). Better results were obtained with Na_2CO_3 (entry 6), and further improvement was achieved with the use of Li_2CO_3 (entry 7). The structure of the *N*,*N*′-dioxide ligand was also found to influence the yield greatly. Chiral *N*,*N*′-dioxide ligands **L2** and **L3** derived from L-pipecolic acid and L-proline, respectively, gave lower reactivities than ligand **L1** derived from L-ramipril (entries 8 and 9 vs 7). No product was observed with aniline-derived *N*,*N*′-dioxide ligand **L4** instead of the bulky and electron-rich 2,6-diisopropylaniline-derived one (entry 10). These results showed that the subunits of the supporting ligand could fine-tune the Lewis acidity and the spatial environment of the catalyst in concert. When 50.0 μL of **2a** was used as both the solvent and reagent, the reaction was obviously improved, giving the product **4a** in 90% yield with 95% ee within 24 h (entry 11). Changing the ligand/metal ratio to 1:1.2 further improved the reactivity, giving almost quantitative yield with a shorter reaction time (entry 12). Remarkably, excellent outcomes were still obtained when the catalyst loading was reduced to 5 mol % (entry 13).

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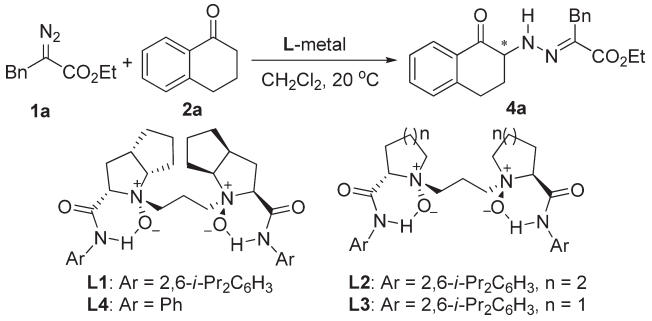
Table 1. Optimization of the Reaction Conditions[a]



entry	L	metal	base	t (h)	yield (%)[b]	ee (%)[c]
1	**L1**	$Sc(OTf)_3$	–	72	21	95
2	**L1**	$Y(OTf)_3$	–	72	0	–
3	**L1**	$La(OTf)_3$	–	72	0	–
4	**L1**	$Sc(OiPr)_3$	–	72	0	–
5	**L1**	$Sc(OTf)_3$	K_2CO_3	72	33	95
6	**L1**	$Sc(OTf)_3$	Na_2CO_3	72	68	95
7	**L1**	$Sc(OTf)_3$	Li_2CO_3	72	85	95
8	**L2**	$Sc(OTf)_3$	Li_2CO_3	72	42	95
9	**L3**	$Sc(OTf)_3$	Li_2CO_3	72	6	80
10	**L4**	$Sc(OTf)_3$	Li_2CO_3	72	0	–
11[d]	**L1**	$Sc(OTf)_3$	Li_2CO_3	24	90	95
12[e]	**L1**	$Sc(OTf)_3$	Li_2CO_3	15	99	95
13[e,f]	**L1**	$Sc(OTf)_3$	Li_2CO_3	24	98	95
14[e,g]	**L1**	$Sc(OTf)_3$	Li_2CO_3	24	45	95

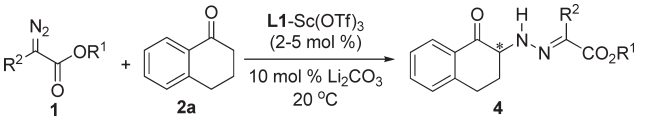
[a] Unless otherwise noted, reactions were performed with 1:1 **L**/metal (10 mol %), base (0 or 10 mol %), **1a** (0.1 mmol), and **2a** (0.1 mmol) in CH_2Cl_2 (0.2 mL) at 20 °C. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Using 50.0 μL of **2a** without CH_2Cl_2. [e] Using 50.0 μL of **2a** without CH_2Cl_2; 1:1.2 **L**/$Sc(OTf)_3$. [f] Using 5 mol % catalyst. [g] Using 2 mol % catalyst.

The enantioselectivity was maintained even when the catalyst loading was decreased to 2 mol %, albeit with a loss of reactivity (entry 14).

With the optimized conditions in hand (Table 1, entry 13), we explored the scope of the reaction. The ester group of the α-diazoester and the position and electronic nature of the substituents on the α-benzyl group of the α-diazoester had no obvious influence on the results (Table 2, entries 1−8). Also, 2-naphthylmethyl-substituted α-diazoester could be employed in this reaction with excellent enantioselectivity and yield (entry 9). α-Diazoesters bearing an aliphatic side chain were applicable in the process (entries 10 and 11). Moreover, allyl and alkynyl groups were well-tolerated in this system (entries 12 and 13). Notably, the α-aryl-substituted α-diazoester was found to be a suitable substrate, providing the adduct in 85% yield with 97% ee after a prolonged reaction time (entry 14). Gram-scale quantities of α-diazoester **1a** (1.03 g, 5.0 mmol) could be used successfully, yielding the product **4a** in 95% yield with 95% ee (values in parentheses in entry 1).

Subsequently, the broad spectrum of α-alkyl ketones as nucleophiles was probed (Table 3). Regardless of the positions and electronic properties of the substituents on the benzene ring of 1-tetralone derivatives **2b**−**g**, excellent yields and ee values were obtained, except that 6-methoxy-1-tetralone (**2c**) displayed

Table 2. Scope of the α-Diazoester in the Catalytic Asymmetric C−N Bond Formation[a]



entry	R^1	R^2	t (h)	yield (%)[b]	ee (%)[c]
1[d]	Et	Bn	24	98 (95) (**4a**)	95 (95) (*S*,*E*)
2	Me	Bn	30	81 (**4b**)	93
3	*i*-Pr	Bn	27	95 (**4c**)	93
4	Et	2-$MeC_6H_4CH_2$	24	93 (**4d**)	92
5	Et	3-$MeC_6H_4CH_2$	24	95 (**4e**)	95
6	Et	4-$MeC_6H_4CH_2$	27	92 (**4f**)	96
7	Et	4-$BrC_6H_4CH_2$	25	98 (**4g**)	97
8	Et	4-$NO_2C_6H_4CH_2$	26	95 (**4h**)	96
9	Et	2-$NpCH_2$	24	92 (**4i**)	97
10	Et	Et	35	80 (**4j**)	93
11	Et	*n*-Bu	26	89 (**4k**)	93
12	Et	allyl	20	90 (**4l**)	91
13[e]	Et	propargyl	26	92 (**4m**)	95
14	Et	Ph	56	85 (**4n**)	97

[a] Unless otherwise noted, reactions were performed with 1:1.2 **L1**/$Sc(OTf)_3$ (5 mol %), Li_2CO_3 (10 mol %), **1** (0.1 mmol), and 50.0 μL of **2a** at 20 °C for the indicated times. [b] Isolated yields. [c] Determined by chiral HPLC. [d] The configuration of **4a** was determined to be (*S*,*E*) by X-ray crystallographic analysis. The results in parentheses were obtained when the model reaction was run on a gram scale: **1a** (1.03 g, 5.0 mmol) and **2a** (2.50 mL) yielded **4a** (1.37 g, 95% yield, 95% ee). [e] Using 2 mol % catalyst.

moderate reactivity (entries 1−6). In addition, chroman-4-one (**2h**) and thiochroman-4-one (**2i**) were good candidates and yielded the products with 98% ee in yields of 75 and 90%, respectively (entries 7 and 8). Next, other benzo cyclic ketones were applied in the current system. 1-Indanone (**2j**) incorporating a five-membered ring was compatible with this method, giving a moderate yield with good enantioselectivity (entry 9), whereas a higher yield (98%) and enantioselectivity (99% ee) were obtained using 1- benzosuberone (**2k**) as the nucleophile (entry 10). Non-benzo cycloalkanones such as cyclohexanone (**2l**) and 4-thiacyclohexanone (**2m**), were used in this process, giving the enantioenriched products in good yields (entries 11 and 12). Moreover, seven-, eight-, and ten-membered aliphatic cyclic ketones were tolerated in this transformation, delivering the corresponding products with modest enantioselectivities, although cyclooctanone exhibited relatively lower reactivity (entries 13−15). It should be noted that this strategy could also be extended to the use of propiophenone (**2q**), which afforded the desired product with moderate enantioselectivity and yield (entry 16).

The issue of concern is how the α-diazoester emerges as the electrophile attacked by the inactive ketone under such mild conditions. Some control experiments were performed to probe the mechanism (Scheme 2). Neither the aryldiazonium salt used in the Japp−Klingemann reaction nor diphenyldiazomethane showed reactivity under the current reaction conditions (eq 1 in Scheme 2). The effect of the ester group of the diazoester was further investigated. Only a trace amount of product was obtained when the highly sterically hindered *tert*-butyl ester instead of the

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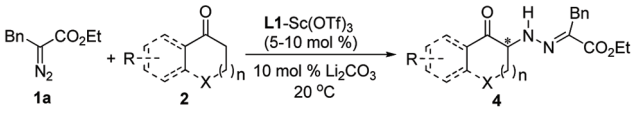
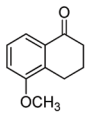
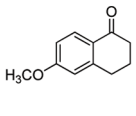
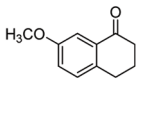
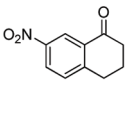
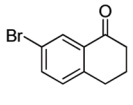
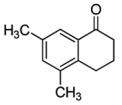
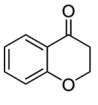
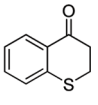
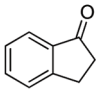
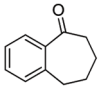
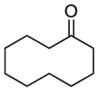
Table 3. Scope of the Ketone in the Catalytic Asymmetric C−N Bond Formation[a,b,c]



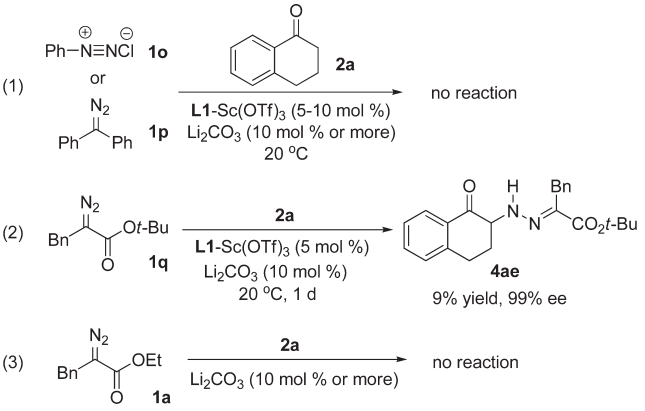
1 (**2b**)	2 (**2c**)	3 (**2d**)	4 (**2e**)
			
89% yield 95% ee	65% yield 93% ee	93% yield 99% ee	88% yield 94% ee
5 (**2f**)	6 (**2g**)	7[d] (**2h**)	8 (**2i**)
			
96% yield 99% ee	80% yield 99% ee	75% yield 98% ee	90% yield 98% ee
9 (**2j**)	10 (**2k**)	11 (**2l**)	12 (**2m**)
			
53% yield 89% ee	98% yield 99% ee	83% yield 71% ee	70% yield 61% ee
13 (**2n**)	14[d] (**2o**)	15 (**2p**)	16[d] (**2q**)
			
81% yield 74% ee	45% yield 77% ee	75% yield 52% ee	45% yield 66% ee

[a] Unless otherwise noted, for substrates **2b**−**2g**, **2j**, **2l**, and **2m**, **1a** (0.1 mmol), **2** (0.2 mmol, 2.0 equiv), 1:1.2 **L1**/Sc(OTf)$_3$ (5 mol %), Li_2CO_3 (10 mol %) and CH_2Cl_2 (50.0 μL) at 20 °C; for others, **1a** (0.1 mmol), **2** (50.0 μL), 1:1.2 **L1**/Sc(OTf)$_3$ (5−10 mol %), and Li_2CO_3 (10 mol %) at 20 °C. [b] Isolated yields are shown. [c] The ee's were determined by chiral HPLC. [d] Using 10 mol % catalyst.

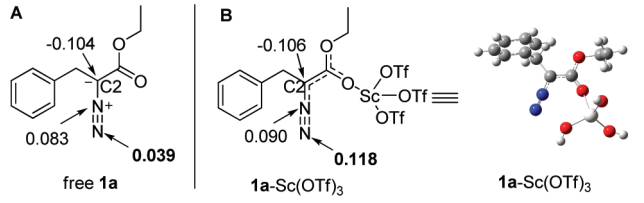
ethyl ester was used (eq 2 in Scheme 2). These results imply that the ester group may be necessary for the activation of the diazoester by coordinating to the Sc catalyst to promote the reaction. The base Li_2CO_3 by itself could not initiate the reaction (eq 3 in Scheme 2), which further confirmed that the activation of the scandium complex to the substrates was crucial for the reaction to occur. In view of the much lower nucleophilicity of ketone **2** than the organolithium reagents used in the previous work,[6] the change of the α-diazoester in the system should be considered as the key factor for the occurrence of the reaction.

Primary theoretical calculations were also performed to give useful information for this uncommon reaction. The results showed that the C2 atom in free α-alkyl-α-diazoester **1a** has strongly negative charge (−0.104) and that the terminal nitrogen of the diazo has a less positive charge (0.039) than the

Scheme 2. Control Experiments



Scheme 3. Natural Bond Orbital Charges of Free 1a and the 1a−Sc(OTf)$_3$ Complex Computed at the B3LYP/6-31G* Level



neighboring nitrogen (0.083) (Scheme 3A). However, when the carbonyl oxygen of the diazoester combines with the strong Lewis acid Sc(OTf)$_3$, the positive charge on the terminal nitrogen atom greatly increases (from 0.039 to 0.118) and exceeds that on the neighboring nitrogen atom (Scheme 3B). On the contrary, the C-nucleophilicity of the α-diazoester changes little after the activation (from −0.104 to −0.106). These results indicate that the electrophilicity of the α-diazoester is greatly increased through activation of the scandium complex and thus promotes this unusual reaction.[11]

In summary, we have described for the first time the electrophilic capability of α-diazoesters in a unique catalytic asymmetric C−N bond formation reaction via α-hydrazonation of unactive ketones. Remarkably, in the presence of an *N,N′*-dioxide−scandium complex, a wide range of α-diazoesters and ketones underwent the reaction smoothly, providing the chiral nitrogen-containing products in excellent yields (up to 98%) and enantioselectivities (up to 99% ee) under mild conditions. Preliminary experiments and theoretical calculations were carried out to explain the unusual process. Application of the electrophilic capability of α-diazoesters will open up a novel way to access the diversity of diazo chemistry. Extension of this work to other related systems and studies of further reactions of the products, especially cleavage of the N−N bond,[12] are currently underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and analytic data (NMR, HPLC and ESI-HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For details, see the Supporting Information (SI). Also, a proposed catalytic model is outlined in the SI.

(12) A further synthetic transformation of the chiral product is described in the SI. Straightforward approaches to N−N bond cleavage (i.e., SmI_2) resulted in a complex mixture of products. Further study of the N−N bond cleavage to get α-amino derivatives is currently underway.