Organocatalysis

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Construction of Enantiomerically Enriched Diazo Compounds Using Diazo Esters as Nucleophiles: Chiral Lewis Base Catalysis**

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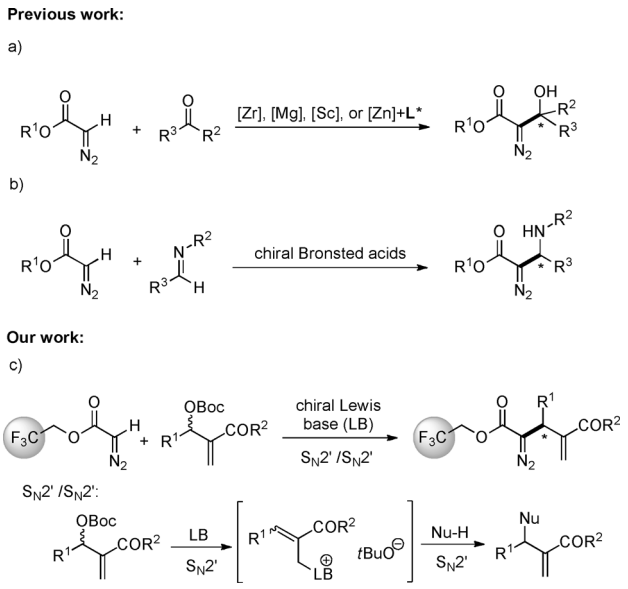
Diazo compounds are remarkably versatile metal carbene precursors which participate in metal-catalyzed rearrangements, cycloadditions, X–H (X = C, N, O, Si, S, etc.) bond insertions, and ylide-forming reactions with concomitant expulsion of N_2.[1] These compounds also take part in 1,3-dipolar cycloaddition reactions of a wide range of dipolarophiles with retention of the CN_2 moiety.[2] Because of their unique properties and extensive applications, the interest in the chemistry of diazo compounds has been long standing.[1e,3] However, efficient synthesis of chiral diazo compounds, especially those with delicate functionalities, is still in urgent need.[4] Enantioselective C–C bond formation employing diazo esters as nucleophilic reaction partners provides a straightforward approach to chiral diazo compounds.[5] Nevertheless, the instability of the diazo moiety to transition metals[1,6] renders them unmanageable in organometallic catalysis, and the nature of the esters makes them less reactive in organocatalysis.[7,8] Until now, the described successful examples are focused on aldol[8,9]/Mannich-type[10] reactions under the catalysis of chiral zirconium,[9a] magnesium,[8a] scandium,[9b] and zinc[9c] complexes or chiral Brønsted acids with simple electrophiles, such as carbonyl compounds and imines (Scheme 1 a,b). Exploitation of diazo esters as nucleophiles in asymmetric catalysis remains a significant challenge.

Recently, chiral Lewis bases were used to catalyze asymmetric allylic alkylation, with Morita-Baylis–Hillman (MBH) adducts as electrophiles, through a S_N2'/S_N2' cascade and has emerged as a powerful strategy for the construction of multifunctional compounds.[11] To expand the number of reactions using diazo esters as nucleophiles, and also in conjunction with our efforts on asymmetric transformations of modified MBH esters,[12] we describe herein our results on chiral Lewis base catalyzed allylic alkylation of diazo esters with MBH carbonates (Scheme 1 c). The desired diazo compounds could be synthesized in good yields with excellent enantioselectivities (up to 96% *ee*), even on a preparative scale. We also demonstrate the utility of these diazo compounds by expedient the synthesis of a number of optically pure N heterocycles.



Scheme 1. Asymmetric reactions using diazo esters as nucleophiles. a) Enantioselective aldol-type reactions of diazo esters with carbonyl compounds catalyzed by chiral Lewis acids (groups of Wang, Feng, Cozzi, and Trost).[8,9] b) Enantioselective Mannich-type reactions of diazo esters with imines catalyzed by chiral Bronsted acids (groups of Terada and Maruoka).[10] c) Chiral Lewis base catalyzed allylic alkylation of diazo esters with MBH carbonates. Boc = *tert*-butoxycarbonyl.

Initial examination was carried out by using ethyl diazoacetate (EDA; **2a**; 0.10 mmol) and the MBH carbonate **3a** (0.12 mmol) in the presence of DABCO (20 mol%) in 0.5 mL THF at room temperature. The corresponding racemic product was isolated in 95% yield (Table 1, entry 1). Encouraged by this preliminary result, we examined a number of chiral tertiary amines for enantioinduction of the reaction. This effort led to the identification of **1e**, which provided access to **4aa** in 91% *ee* even though the yield (35%) remained relatively low (Table 1, entry 6). To increase the reaction yield and enantioselectivity, various solvents were screened with catalyst **1e**. The experimental results revealed that increased solvent polarity led to an increased yield.

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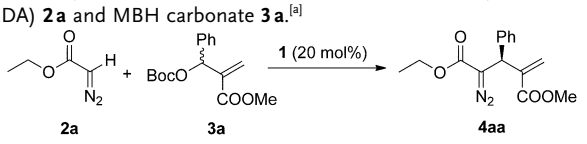
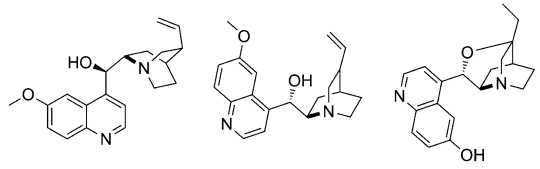
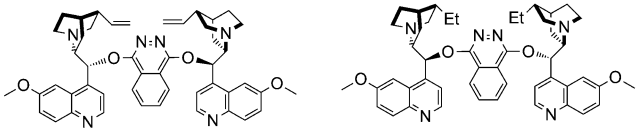
Table 1: Optimization of the reaction conditions with ethyl diazoacetate (EDA) **2a** and MBH carbonate **3a**.[a]



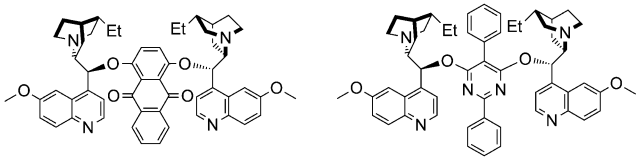
2a **3a** **4aa**



1a **1b** **1c**



1d **1e**



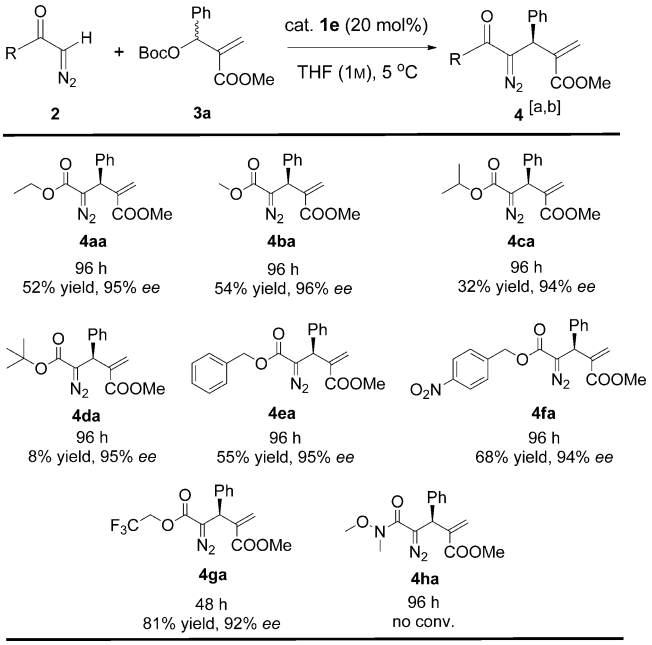
1f **1g**

Entry	Cat.	Solvent	*T* [°C]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	DABCO	THF	25	1	95	–
2	**1a**	THF	25	36	<10	15
3	**1b**	THF	25	36	<10	−30[d]
4	**1c**	THF	25	36	61	−24[d]
5	**1d**	THF	25	36	<10	−38[d]
6	**1e**	THF	25	36	35	91
7	**1f**	THF	25	36	45	86
8	**1g**	THF	25	36	<10	−8[d]
9	**1e**	toluene	25	36	trace	n.d.
10	**1e**	1,4-dioxane	25	36	33	90
11	**1e**	ethyl acetate	25	36	27	85
12	**1e**	CH_2Cl_2	25	36	34	75
13	**1e**	acetone	25	36	65	72
14	**1e**	acetonitrile	25	36	75	26
15	**1e**	THF	60	36	trace	n.d.
16	**1e**	THF	5	96	40	95
17	**1e**	THF	−10	96	14	96
18	**1e**	THF	5	96	52	95[f]
19	**1e**	THF	5	96	38	94[e,f]

[a] Unless otherwise noted (except entry 1), the reaction was carried out with 0.10 mmol of **2a** (0.20 M), 0.30 mmol of **3a**, 20 mol% of catalyst **1** (0.02 mmol). [b] Yield of isolated product. [c] The *ee* values were determined by HPLC analysis using chiral stationary phase. [d] The opposite configuration. [e] 10 mol% of catalyst **1e** was used. [f] Increase the concentration of reactants to 1.0 mol/L. DABCO = 1,4-diazabicyclo-[2.2.2]octane, n.d. = not determined, THF = tetrahydrofuran.

However, this was associated with reduced enantioselectivity of the reaction (Table 1, entries 9–14). Whereas elevated reaction temperature caused an alternative 1,3-dipolar cycloaddition reaction pathway to predominate (Table 1, entry 15), the enantioselectivity of the desired transformation could be improved to 95% *ee* by carrying out the reaction at 5°C (Table 1, entry 16). Further decrease of reaction the temperature led to low substrate conversion even with a prolonged reaction time (Table 1, entry 17). The yield could be somewhat improved without loss of enantioselectivity of the reaction when it was carried out at an increased concentration of the reactants (Table 1 entries 16 verus 18).

To further increase the efficiency of the reaction, a number of diazo esters were synthesized and their effect on the reaction was evaluated (Scheme 2). Under the above optimized reaction conditions, the product **4da** was obtained in low yield when *tert*-butyl diazo acetate (**2d**) was employed, thus suggesting a bulky ester group to be detrimental to the reaction. In anticipation that modulation of the electronic property of the ester group of the substrate might lead to increased reaction efficiency, 4-nitrobenzyl diazo acetate (**2f**) was prepared and subjected to the reaction conditions. Indeed, **4fa** was obtained in 68% yield. Considering fluorine-containing groups might significantly modify the chemical and biological properties of organic molecules,[13] we designed and synthesized the 2,2,2-trifluoroethyl diazo acetate (**2g**), which contains a strong electron-withdrawing moiety (CF_3). Further increase of reaction efficiency was observed when **2g** was used to give **4ga** in 81% yield. No product was observed when 2-diazo-*N*-methoxy-*N*-methyl-acetamide (**2h**), with an electron donor, was employed in the reaction.



Scheme 2. Screening for the optimal diazo ester. [a] Unless otherwise noted, the reaction was carried out with 0.10 mmol of **2**, 0.30 mmol of **3a**, 20 mol% of **1e** (0.02 mmol) in THF (0.1 mL) at 5°C. [b] Yield of isolated product. The *ee* values were determined by HPLC analysis using chiral stationary phase. The absolute configurations of **4aa**–**4ga** were assigned by comparing their circular dichroism spectra with that of **4gg**.

Based on the above results, we reasoned that substituting the ethyl group of EDA with a 2,2,2-trifluoroethyl group

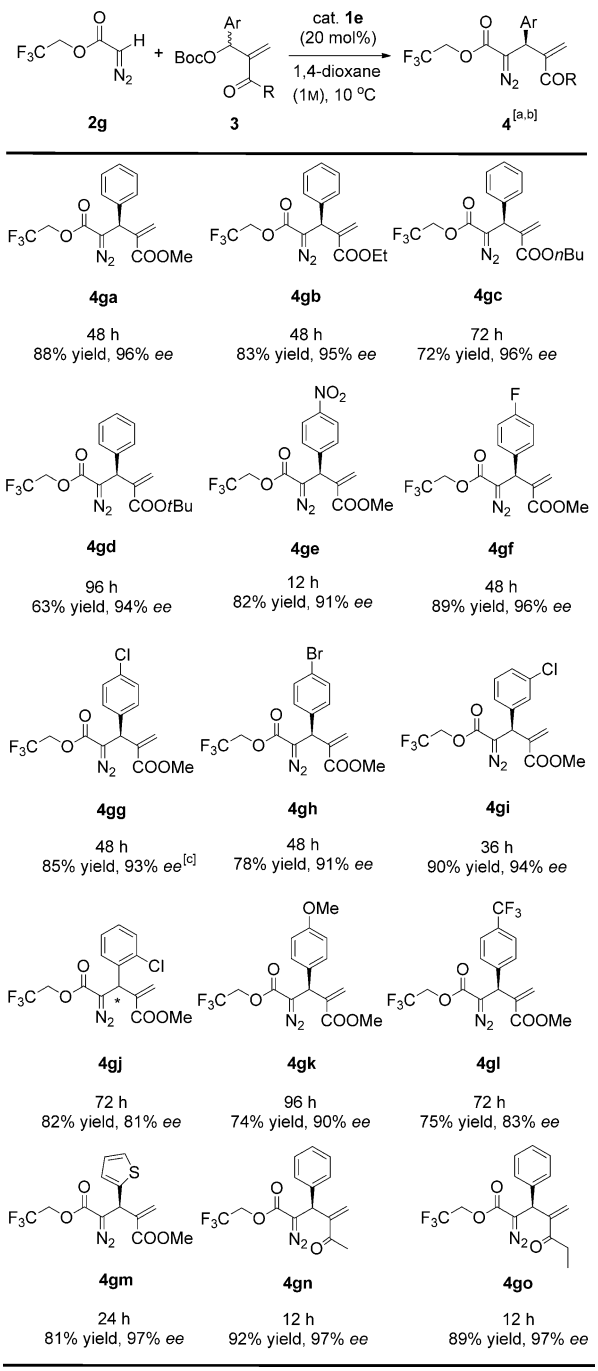
(TFEDA) increased the efficiency of the reaction as a result of the enhanced acidity of the α proton of the diazo ester. This hypothesis was clearly demonstrated in an H/D exchange experiment. The incubation of TFEDA with D_2O for 4 hours led to 91% α-hydrogen exchange with deuterium at ambient temperature. However, only 20% deuterium incorporation was observed when EDA reacted with D_2O under the same reaction conditions (see the Supporting Information for further details).

Having established the diazo ester **2g** as the optimal substrate, we further evaluated the reaction conditions using the MBH carbonate **3a** (see Table 2 in the Supporting Information). A number of solvents having low polarity were screened. Good yields ranging from 74% to 85% were obtained in all the solvents that were studied, with 1,4-dioxane being the best solvent, thus leading to formation of **4ga** in 85% yield and 92% *ee*. The yield of **4ga** reduced slightly when 2 equivalents of the MBH carbonate **3a** was used. Finally, execution of the reaction at 10°C for 48 hours led to the optimal yield (88%) and *ee* value (96%) of the reaction.

With the optimized reaction conditions in hand, we examined an array of MBH carbonates (**3**) to explore the generality of this asymmetric transformation. The reactions were conducted in 0.1 mL of 1,4-dioxane with 20 mol% of the catalyst **1e** at 10°C. The results are summarized in Scheme 3. The scope of the reaction could be successfully extended to MBH carbonates with various substituents, and high enantioselectivities were generally achieved (**4ga**–**4gd**). Moreover, the electronic properties of the phenyl ring of the MBH carbonates appeared to slightly influence the level of the enantioselectivity and most of the MBH carbonates participated in this process with high efficiency (**4ge**–**4gl**). When the 2-thienyl-substituted MBH carbonate was used as the substrate, the asymmetric transformation proceeded with 97% *ee* (**4gm**). MBH carbonates derived from an alkyl vinyl ketone could also be transformed with a good *ee* values under the same reaction conditions (**4gn**–**4go**).

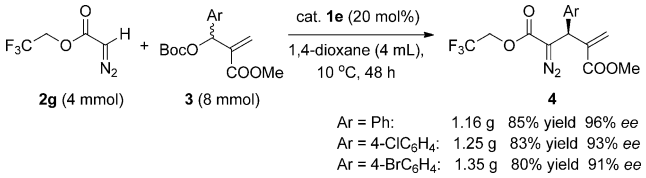
The reaction was also performed on large scale to test its scalability and the results are illustrated in Scheme 4. When the reactions were conducted at 4 mmol, highly enantioselective (91–96% *ee*) α-allylic diazo esters could be prepared in excellent yields (80–85%).

The functionalities of **4** provide opportunities for further manipulation to give products of increased complexity. Some of these potential utilities were demonstrated in the synthesis of optically pure N heterocycles as shown in Scheme 5. The *t*BuOK-catalyzed nucelophilic thiol conjugate addition of **4gg** and subsequent cyclization of the resulting α-carbanion intermediate with the diazo group gave the diastereomeric pyrazolines **5** and **6** without any racemization (Scheme 5a).[14] The absolute configuration at C2 of the pyrazoline ring was determined to be *S* by X-ray diffraction of the NTs derivative (**7**) of **5**.[15] In the presence of 1 equivalent acetic acid, the diazo group of **4ga** could only be partially reduced by platinum-catalyzed hydrogenation. This reduction was accompanied by intramolecular cyclization and reduction of the exocyclic alkene to afford the *cis*-dihydropyridazinone derivative **8** (Scheme 5b).[16] Interestingly, different products

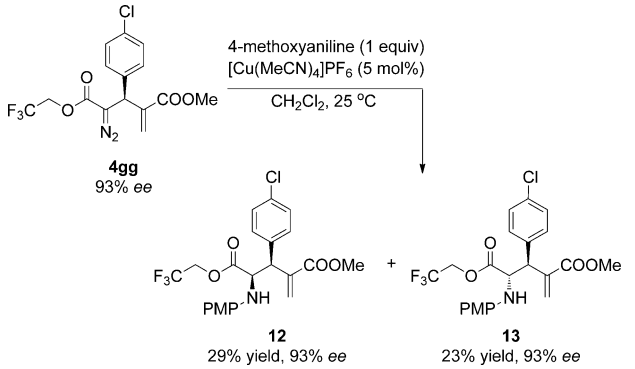


Scheme 3. Asymmetric allylic alkylation of TFEDA (**2g**) with MBH carbonates **3**. [a] The reaction was carried out with 0.10 mmol of **2g**, 0.20 mmol of **3**, 20 mol% of **1e** (0.02 mmol) in 1,4-dioxane (0.1 mL) at 10°C. [b] Yield of isolated product. The *ee* values were determined by HPLC analysis using chiral stationary phase. [c] The absolute configuration of **4gg** was determined to be *S* by comparison to its derivative **7**, and those of the other products were assigned by comparing their circular dichroism spectra with that of **4gg**.

were formed when **4gg** was treated with different mole ratios of SmI_2. Upon treatment with 3 equivalents of SmI_2, **4gg** was converted into *trans/cis* (1:5) mixtures of tetrahydropyridazine derivatives upon partial reduction of the diazo group accompanied by intramolecular conjugate addition. Upon treatment of **4gg** with 6 equivalents of SmI_2, the diazo group

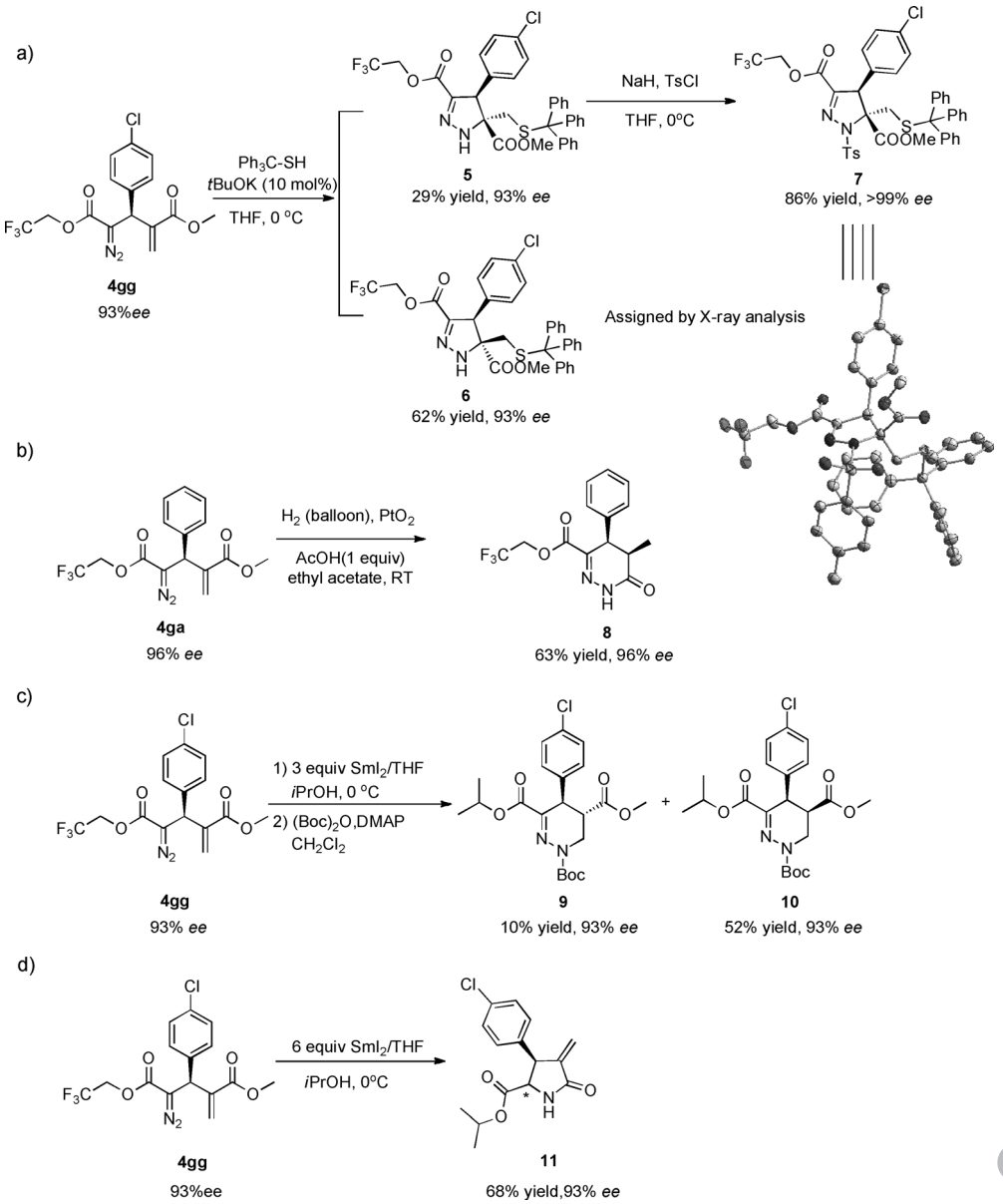


Scheme 4. Gram-scale reaction for the preparation of the optically pure α-allylic diazo esters **4**.



Scheme 6. PMP = *para*-methoxyphenyl.

was fully reduced, and the functionalized ketopyrrolidine **11** was formed with high stereoselectivity.[10c] Transesterification with the solvent was observed in both of these two processes (Scheme 5c,d). Additionally, as a metal carbene precursor, **4gg** participated in intermolecular N–H insertion with the copper(I) catalyst $[Cu(MeCN)_4]PF_6$, thus providing the enantioenriched α-amino acid derivatives **12** and **13** (Scheme 6).[17]



Scheme 5. The synthesis of optically pure N Heterocycles derived from the chiral α-allylic diazo esters **4**. DMAP = 4-(dimethylamino)pyridine, Ts = 4-toluenesulfonyl.

In summary, we have established a process for asymmetric allylic alkylation of diazo esters under the catalysis of modified cinchona alkaloids. Highly functionalized diazo compounds could be synthesized in good yields with excellent enantioselectivities. We demonstrated the utility of the products by rapid synthesis of a number of optically pure N heterocycles. The successful development of this process partially builds upon our discovery of 2,2,2-trifluoroethyl diazoacetate (TFEDA) as a superior nucleophilic reagent. This discovery potentially opens up new possibilities for the development of other transformations involving on diazo esters as nucleophilic reagents. Further exploration of other such transformations of diazo esters is now in progress in our laboratory.

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Keywords: diazo compounds · fluorine · heterocycles · organocatalysis synthetic methods

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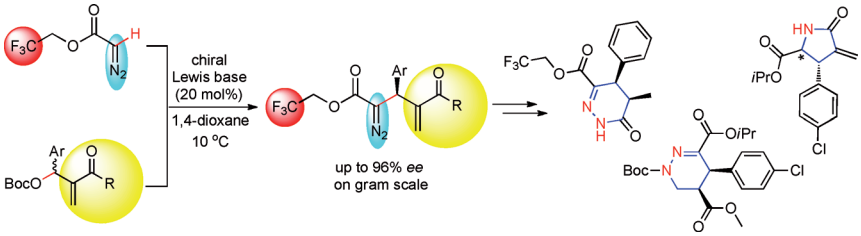
Communications

Organocatalysis

H. Mao, A. Lin, Y. Shi, Z. Mao, X. Zhu, W. Li, H. Hu, Y. Cheng, C. Zhu* ——— ■■■■–■■■■

Construction of Enantiomerically Enriched Diazo Compounds Using Diazo Esters as Nucleophiles: Chiral Lewis Base Catalysis



Amazing diazo: The title reaction leads to highly functionalized diazo compounds in good yields with excellent enantioselectivities (see scheme; Boc = *tert*-butoxycarbonyl). The utility of the products was demonstrated by the rapid synthesis of a number of optically pure nitrogen heterocycles. The key to this process was the use of 2,2,2-trifluoroethyl diazoacetate as a superior nucleophilic reagent.