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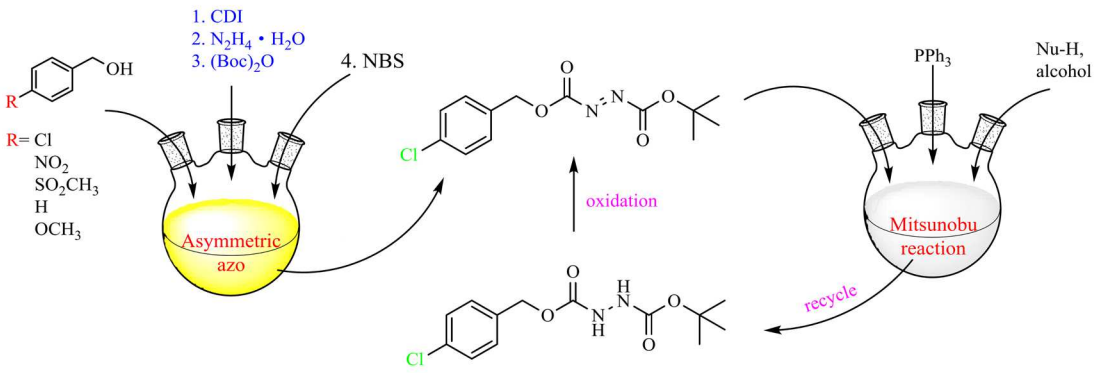

Graphical Abstract

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Synthesis and application of a novel asymmetric azo Reagent: 1-(tert-butyl)-2-(4-chlorobenzyl) azodicarboxylate (tBCAD)

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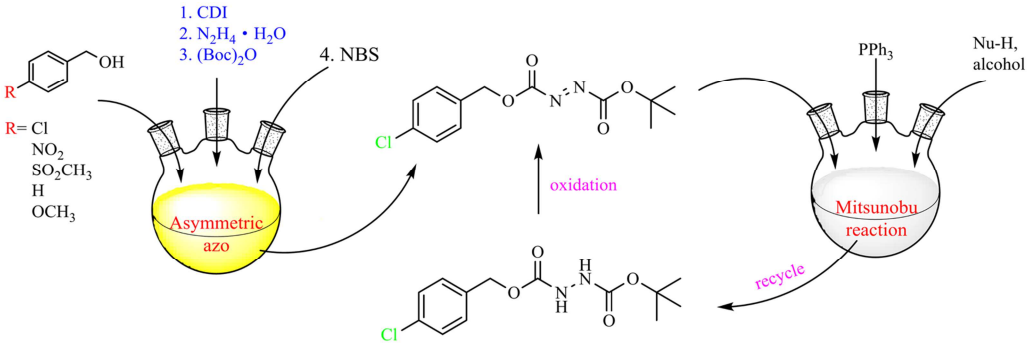

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Synthesis and application of a novel asymmetric azo reagent: 1-(tert-butyl)-2-(4-chlorobenzyl) azodicarboxylate (tBCAD)

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ABSTRACT

A series of novel asymmetric azo reagents, 1-(*tert*-butyl)-2-(4-substituted benzyl) azodicarboxylate, were prepared. The synthetic process has the advantange of simpleness, easy operation, mild reaction condition and high yield. The 1-(*tert*-butyl)-2-(4-chlorobenzyl) azodicarboxylate (tBCAD) was selected for its stability and convenience to handle, and its precursor can be recycled by recrystallization with toluene. The *t*BCAD and DIAD were applied to a wide variety of Mitsunobu reactions. The experimental results showed that the performance of tBCAD in Mitsunobu reaction was comparable to that of DIAD, while the stability of tBCAD was much better than DIAD. Thus, tBCAD can be a novel, stable, effective azo-reagent for the Mitsunobu reaction.

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1. Introduction

Mitsunobu reaction refers to the reaction of a primary or secondary alcohol with a nucleophile in the presence of triarylphosphine or trialkylphosphine and an azo reagent.[1,2] Since its first discovery in 1967 by the Japanese chemist Oyo Mitsunobu,[3,4] the Mitsunobu reaction has found a wide range of applications due to its stereoselectivity, versatility, effectiveness and mild reaction condition, especially in the field of pharmaceutical industry.[5-8] The application of Mitsunobu reaction, initially used for synthesizing esters, was gradually extended to the domain of ammonias, azides, ethers, thioesters and thioethers, etc.[9] Azo reagents, as an inevitable component of Mitsunobu reaction have aroused great attention. Traditionally, diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) is the appropriate and universal alternative, though other reagents have been developed and reported with excellent results (Fig. 1).[10-15] Despite the widespread usage of DEAD and DIAD, conventional azo-reagents can still be problematic: they (a) are unstable in the absence of solvent, light, heat or even collision, (b) are difficult to separate hydrazine by-products, (c) are not usually amenable to recycle and (d) exist explosion hazards.[16-19] Research aimed at solving these drawbacks and discovering better, stable and non-hazard azo reagents has been a hit since then.

After carefully studying the related literatures on newly developed azo reagents and phosphine reagents,[20-25] we found, however, that asymmetrical azo reagents were rarely reported. Only Sivaraman Dandapani and Dennis P. Curran reported F-DEAD-2, and Daniel P. Furkert's group synthesized ACCs.[14,15] Both F-DEAD-2 and ACCs displayed unique properties compared to the symmetric ones with similar structure. Therefore, we designed a new synthetic route to produce a series of modified novel asymmetric azo reagents to testify our hypothesis. Among those, the best one is 1-(tert-butyl)-2-(4-chlorobenzyl) azodicarboxylate (tBCAD), which has similar reactivity to DIAD, while possessing unique advantages, including easy handling, as a pure stable solid, facile separation and preeminent recycling capability. Herein we present a detailed report on the synthesis of tBCAD.

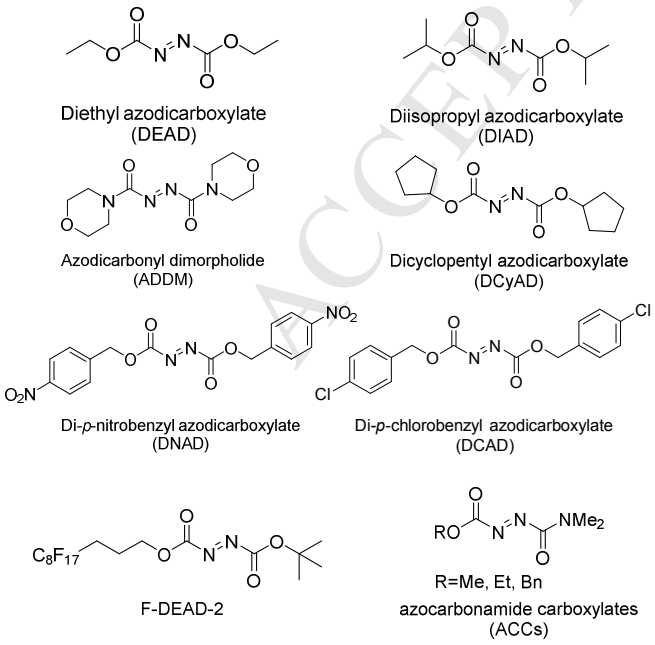
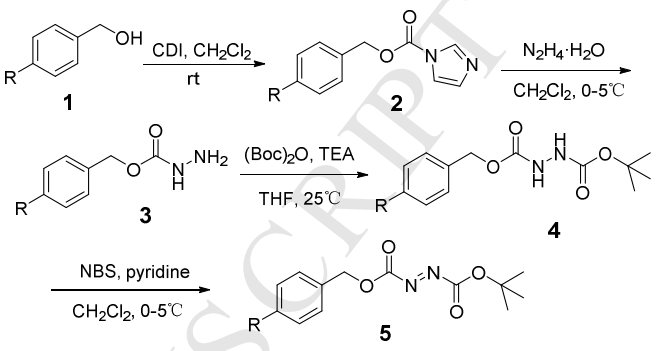


Fig. 1. Mitsunobu reagents

2. Results and Discussion

2.1. The synthesis methodology and properties of azo reagents

The traditional azo reagents (DEAD, DIAD) are synthesised by first intermixing alkyl chloroformate with hydrazine. Alkyl chloroformates are prepared by mixing the alkyl alcohols with phosgene. However, considering the toxicity of phosgene and alkyl chloroformate, we selected *N*, *N'*-carbonyldiimidazole (CDI) as a substitute for phosgene.



a R=Cl; **b** R=NO_2; **c** R=SO_2CH_3; **d** R=H; **e** R=OCH_3

Scheme 1. The Synthetic route of asymmetric azo reagents

Table 1. The products, reaction time and corresponding yields of each synthetic step

N	R	product	time/h	yield/%
1	Cl	**2a**	1	-
2		**3a**	1.5	89.1[a]
3		**4a**	5	86.6
4		**5a**	2	96.0
5	NO_2	**2b**	1	-
6		**3b**	1.5	85.7[a]
7		**4b**	5	80.4
8		**5b**	2	96.8
9	SO_2CH_3	**2c**	1	-
10		**3c**	1.5	85.1[a]
11		**4c**	5	86.9
12		**5c**	2	91.8
13	H	**2d**	1	-
14		**3d**	1.5	86.9[a]
15		**4d**	5	84.8
16		**5d**	2	98.5
17	OCH_3	**2e**	1	-
18		**3e**	1.5	94.4[a]
19		**4e**	5	84.0
20		**5e**	2	98.6

[a] The total yield of the first two steps.

The synthetic route used in this article (scheme 1) is safe and environmentally friendly, while simple to operate with high-yield. The first step adopted *N*, *N'*-carbonyldiimidazole (CDI), which was solid with low toxicity. The reaction condition was not rigorous. Room temperature would make it happen. The second step was ice water bathing, which operated with no difficulty.[26-28] The total yield of the two steps was 89.1% (R=Cl). The workup was simply by washing the reaction solution with pure water. The yield of the third step was 86.6 % (R=Cl), which was

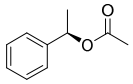
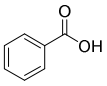
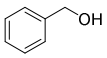
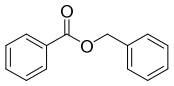
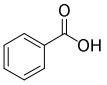
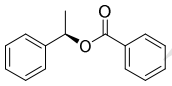
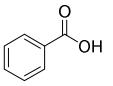
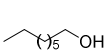
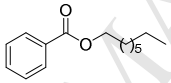
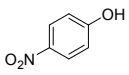
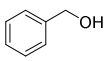
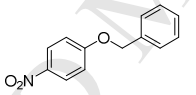
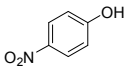
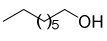
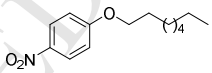
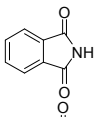
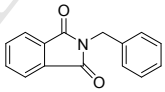
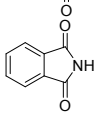
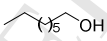
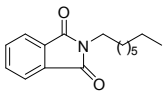
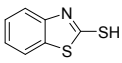
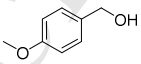
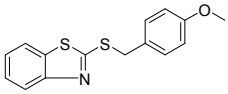
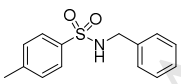
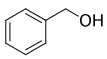
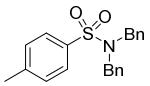
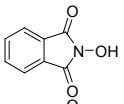
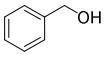
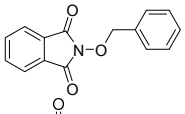
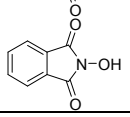
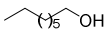
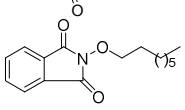
comparable to that of other reported symmetric azo regents.[11,12] Similarly, more asymmetric azo reagents can be conveniently synthesized by introducing different substituents on the side of **3**. Finally, the last step yield was almost quantitative. The detailed results were given in Table 1.

The five azo reagents were exposed to the air at room temperature. Their decomposition was monitored by TLC and ^{1}H NMR spectroscopy. Except tBCAD **5a**, the other four azo reagents decomposed to various degrees in 9 days while tBCAD did not disintegrate in 1 month. We also determined the decomposition temperature of tBCAD, which was 154□ by DSC-TGA. Thus, tBCAD was selected as our desired novel asymmetric azo reagent, which was stable at room temperature. Since tBCAD was selected according to the stability, we afterwards, studied the properties of its precursor **4a**. It turned out that the precursor **4a** was a very stable white solid that was simple and convenient for storage and usage. More importantly, the solubility of **4a** in toluene was very low (<0.008 g/mL). Therefore, after tBCAD's employment in the Mitsunobu reaction, **4a** can be recovered by recrystallization with toluene, and the corresponding azo reagent tBCAD was obtained by one more step of oxidation. Finally, we studied the effect of tBCAD in Mitsunobu reaction.

2.2. Effect of 1-tert-butyl-2- (4-chlorobenzyl) azodicarboxylate (tBCAD) in Mitsunobu reaction

The compounds served as nucleophilic precursors in the

Table 2
Comparison of Mitsunobu couplings mediated by DIAD/PPh_3 and tBCAD/PPh_3

Entry	Nu-H	Alcohol	Product	Time/h	Yield/%[a]	
					DIAD	tBCAD
1				10	70[32]	69.5[c,d]
2				3	88.2[b]	90.6[b]
3				4	74.3[b]	76.1[b,d]
4				4	94.9[b]	97.9[b]
5				12	75.9[c]	80.0[c]
6				8	87.2[c]	91.6[c]
7				3.5	83.1[b]	79.7[b]
8				5	88.8[b]	89.6[b]
9				3.5	91.6[b]	87.8[b]
10				5	76.4[c]	78.3[c]
11				6	89.2[c]	90.1[c]
12				5.5	91.3[c]	89.8[c]

[a] Isolated,chromatographically pure material.
[b] These reactions were conducted with alcohol(1.0 equiv), 1.2 equiv of acidic pronuclephile, PPh_3, and azodicarboxylate reagent at rt in CH_2Cl_2 and the isolated yields based on alcohols.
[c] These reactions were conducted with alcohol (1.0 equiv),1.2 equiv of acidic pronuclephile, PPh_3,and azodicarboxylate reagent at rt in THF and the isolated yields based on alcohols.
[d] Determinded by GC analysis with 10% methyl-β-cyclodextrin chiral column.

Mitsunobu reaction are generally acidic compounds containing O-H, S-H, or N-H group. These nucleophilic precursors react with primary alcohols or secondary alcohols forming new C-O C-S or C-N bond in the reaction.[9] 1-(tert-butyl)-2- (4-chlorobenzyl) azodicarboxylate (tBCAD) was adopted as an azo reagent in the Mitsunobu reaction mixed with triphenylphosphine. The results were compared with those of DIAD / PPh_3. After the reaction yields were calculated, the results were given in Table 2.

One of the salient features of the Mitsunobu reaction is that when the secondary carbon attached to the alcoholic hydroxyl group having a chiral center, the chirality is completely reversed via an S_N2 mechanism.[29-31] That has been widely used in pharmaceutical industry and becomes a standard method of chiral flip. [5-7] In this paper, Mitsunobu reaction was carried out using chiral secondary alcohols (*S*) - (-) - 1-phenylethyl alcohol with acetic acid (Table 2, Entry 1) and benzoic acid (Table 2, Entry 3) to obtain chiral completely inverted products. With tBCAD as the azo reagent, the reaction yielded a yield of 69.5% (90% ee, Entry 1) for 10 h, and the yield of the reaction with DIAD as azo reagent was only 70% (91% ee, Entry 1).[32] Because of steric hindrance, the reactivity of the secondary alcohol was worse than that of the primary alcohol (Table 2, Entry 1-4). The performance of 1-octanol was better than that of benzyl alcohol when the same nucleophilic precursors were used in the Mitsunobu reaction (Table 2, Entry 2, 4, 5, 6, 7, 8, 11, 12). In addition, there was probably a relationship between the product yields with pK_a of the nucleophilic precursors. From the results of Entry 2, 5, 7, 9 and 11, it was deduced that the lower pK_a of the nucleophilic precursors, the higher the yield probably was. As a whole, in Mitsunobu reaction, tBCAD served as a good azo reagent with regard to the yield results, which was comparable with that of DIAD. Considering the stability and safety, however, tBCAD is far better than DIAD, and the former is easy to transport and secure to storage.

3. Conclusion

A series of novel asymmetric azo reagents have been synthesized and a new synthetic route has been developed. The route was simple and facile, easy to operate, and the corresponding yields were high. The required raw materials are easily accessible with a low price. The tBCAD was selected for being very stable at room temperature. Furthermore, its precursor **4a** can be easily recycled by recrystallization with toluene. Finally, it was used in various Mitsunobu coupligs. The results showed that tBCAD's reactivity was comparable with that of DIAD, while its stability is significantly better. And the solid state nature of tBCAD makes it more convenient for transportation, storage and use. Therefore, tBCAD can be used as a new azo reagent, taking place of DIAD in the industrial scale.

4. Experimental

4.1 General

All the chemicals used were reagent-grade, purchased from commercial supplier, and used without further purification. CH_2Cl_2 used in reactions were prepared by distillation with anhydrous Na_2SO_4. THF was dried with molecular sieve. TLC analysis was performed on ZF-20D F_{254} plates. ^1H NMR and ^{13}C NMR spectra were recorded in CD_3Cl or DMSO-d_6 using TMS as an internal standard on a Bruker AVANCE Ⅲ 500 at 500 MHz. Melting points were determined by a WRS-1B digital melting point apparatus. Enantiomeric purities were determined by GC analysis (Fuli9790) using a 10% methyl-β-cyclodextrin chiral column. Elementary analysis was performed by Vario MICRO Cube Elemental Analyzer.

*4.2 General synthetic procedure for hydrazinecarboxylate (**3**)*

Alcohol **1** (40 mmol) was added in portions to the solid-liquid mixture of CH_2Cl_2 (40 mL) and *N, N'*-carbonyldiimidazole (6.95 g, 42 mmol) at room temperature. The solid-liquid mixture turned into a yellowish solution, and was stirred at room temperature for 30 min after feeding. Then the solution was washed with water (2×40 mL). The organic phase was transferred to a three-necked flask, and cooled to 0-5 ℃. Hydrazine hydrate (2.27 g, 44 mmol) was added dropwise and amorphous white solid produced after a while. The mixture was stirred at room temperature for 30 min, and then filtered. The white solid was washed with water. The filtrate was concentrated in vacuo leading to a white solid and filtered. The white solid was also washed with water. Both of the white solid was collected and dried in vacuo to get the product **3**.

*4.2.1. 4-chlorobenzyl hydrazinecarboxylate (**3a**)*. White solid (7.15 g, 89.1%). Mp 127.5-127.8℃.

*4.2.2. 4-nitrobenzyl hydrazinecarboxylate (**3b**)*. White solid (7.24 g, 85.7%). Mp 136.7-137.4℃.

*4.2.3. 4-(methylsulfonyl)benzyl hydrazinecarboxylate (**3c**)*. White solid (8.31 g, 85.1%). Mp 104.6-105.3℃.

*4.2.4. benzyl hydrazinecarboxylate (**3d**)*. White solid (5.78 g, 86.9%). Mp 68.5-69.1℃.

*4.2.5. 4-methoxybenzyl hydrazinecarboxylate (**3e**)*. White solid (7.41 g, 94.4%). Mp 77.0-77.5℃.

*4.3 General procedure for hydrazinedicarboxylate (**4**)*

Di-*tert*-butyl dicarbonate (8.02g, 36mmol) dissolved in THF (10 mL) was added dropwise to the solid-liquid mixture of **3** (30 mmol), TEA (3.64 g, 36 mmol) and THF (15 mL) at 25℃. The mixture was stirred for 5 h. The resulting clear colorless solution was concentrated in vacuo, recrystallizing with CH_2Cl_2 and then filtered. The white solid was washed with petroleum ether and water. The filtrate was washed with 1M HCl (20 mL). Then the organic phase was concentrated and white solid precipitated. The mixture was filtered and the solid was washed with petroleum ether and water. Both of the white solid was collected and dried in vacuo to afford the desired product **4**.

*4.3.1. 1-(tert-butyl)-2-(4-chlorobenzyl) hydrazinedicarboxylate (**4a**)*

White solid (7.79 g, 86.6%). Mp 138.5-139.2℃. ^1H NMR (500 MHz, CD_3Cl) δ 7.34-7.28 (m, 4H, ArH) 6.47 (s, 1H, NH), 6.28 (s, 1H, NH), 5.14 (s, 2H, CH_2), 1.47 (s, 9H, CH_3); ^{13}C NMR (CD_3Cl, 500 MHz): δ 156.77, 155.86, 134.51, 134.39, 129.83, 128.98, 82.18, 67.11, 28.35; Anal. Calcd for $C_{13}H_{17}ClN_2O_4$ (300.74): C 51.92, H 5.70, N 9.32. Found: C 51.70, H 5.66, N 9.35.

*4.3.2. 1-(tert-butyl)-2-(4-nitrobenzyl) hydrazinedicarboxylate (**4b**)*

White solid (7.51 g, 80.4%). Mp 127.5-128.1℃. ^1H NMR (500 MHz, CD_3Cl) δ 8.22 (d, *J*=8.5Hz, 2H), 7.52 (d, *J*=8.5Hz, 2H), 6.61 (s, 1H, NH), 6.34 (s, 1H, NH), 5.28 (s, 2H,CH_2), 1.47 (s, 9H, CH_3); Anal. Calcd for $C_{13}H_{17}N_3O_6$ (311.29): C 50.16, H 5.50, N 13.50. Found: C 49.92, H 5.49, N 13.57.

*4.3.3. 1-(tert-butyl)-2-(4-methylsulfonylbenzyl) hydrazinedicarb-oxylate (**4c**)*

White solid (8.97g, 86.9%). Mp 137.0-138.2□. ^{1}H NMR (500 MHz, CD_3Cl) δ 7.94 (d, *J*=8.0Hz, 2H), 7.60 (d, *J*=8.0Hz, 2H), 6.60 (s, 1H, NH), 6.34 (s, 1H, NH), 5.27 (s, 2H,CH_2), 3.05 (s, 3H, SO_2CH_3), 1.47 (s, 9H, CH_3); Anal. Calcd for $C_{14}H_{20}N_2O_6S$ (344.38): C 48.83, H 5.85, N 8.13. Found: C 48.83, H 5.91, N 8.03.

*4.3.4. 1-(tert-butyl)-2-benzyl hydrazinedicarboxylate (**4d**)*

White solid (6.77 g, 84.8%). Mp 75.0-75.5□. ^{1}H NMR (500 MHz, CD_3Cl) δ 7.36-7.32 (m, 5H, ArH), 6.46 (s, 1H, NH), 6.28 (s, 1H, NH), 5.18 (s, 2H,CH_2), 1.47 (s, 9H, CH_3); Anal. Calcd for $C_{13}H_{18}N_2O_4$ (266.30): C 58.63, H 6.81, N 10.52. Found: C 58.58, H 6.82, N 10.63.

*4.3.5. 1-(tert-butyl)-2-(4-methoxybenzyl) hydrazinedicarboxylate (**4e**)*

White solid (7.47 g, 84.0%). Mp 87.4-87.8□. ^{1}H NMR (500 MHz, CD_3Cl) δ 7.30 (d, *J*=7.5Hz, 2H), 6.88 (d, *J*=7.5Hz, 2H), 6.53 (s, 1H, NH), 6.34 (s, 1H, NH), 5.10 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.46 (s, 9H, CH_3); Anal. Calcd for $C_{14}H_{20}N_2O_5$ (296.32): C 56.75, H 6.80, N 9.45. Found: C 56.66, H 6.78, N 9.52.

*4.4 General synthetic procedure for the azodicarboxylate (**5**)*

N-bromosuccinimide (1.09 g, 5.5 mmol) was added in portions to the mixture of **4** (5 mmol), pyridine (0.45 g, 5.5 mmol) and CH_2Cl_2 (20 mL) at 0□. The reaction mixture turned to yellow upon addition, and was stirred at 0□ for 30 min after addition. Then the reaction solution was washed with 5% citric acid aqueous solution (20 mL×3), 2% NaOH aqueous solution (20 mL×2), water (20 mL). The organic phase was then dried over anhydrous Na_2SO_4 and was concentrated in vacuo to afford the desired product **5**.

*4.4.1. 1-(tert-butyl)-2-(chlorobenzyl) azodicarboxylate (**5a**)*

Orange solid (1.43 g, 96.0%). Mp 46.5-47.5□. ^{1}H NMR (500 MHz, CD_3Cl) δ 7.39 (s, 4H, ArH), 5.39 (s, 2H, CH_2), 1.61 (s, 9H, CH_3); ^{13}C NMR (500 MHz, CD_3Cl) δ 160.50, 159.07, 135.42, 132.37, 130.43, 129.24, 87.51, 69.91, 27.92; Anal. Calcd for $C_{13}H_{15}ClN_2O_4$ (298.72): C 52.27, H 5.06, N 9.38. Found: C 52.13, H 5.16, N 9.43.

*4.4.2. 1-(tert-butyl)-2-(4-nitrobenzyl) azodicarboxylate (**5b**)*

Orange solid (1.52 g, 96.8%). Mp 43.4-44.1□. ^{1}H NMR (500 MHz, CD_3Cl) δ 8.27 (d, *J*=9.0Hz, 2H), 7.61 (d, *J*=8.5Hz, 2H), 5.53 (s, 2H, CH_2), 1.63 (s, 9H, CH_3); ^{13}C NMR (500 MHz, CD_3Cl) δ 160.30, 158.94, 148.42, 140.87, 129.14, 124.22, 87.78, 68.90, 27.92; Anal. Calcd for $C_{13}H_{15}N_3O_6$ (309.28): C 50.49, H 4.89, N 13.59. Found: C 50.14, H 4.94, N 13.48.

*4.4.3. 1-(tert-butyl)-2-(4-methylsulfonylbenzyl) azodicarboxylate (**5c**)*

Orange solid (1.57 g, 91.8%). Mp 88.2-89.5□. ^{1}H NMR (500 MHz, CD_3Cl) 7.99 (d, *J*=8.5Hz, 2H), 7.65 (d, *J*=8.5Hz, 2H), 5.52 (s, 2H, CH_2), 3.06 (s, 3H, SO_2CH_3), 1.63 (s, 9H, CH_3); ^{13}C NMR (500 MHz, CD_3Cl) δ 160.36, 158.97, 141.38, 139.94, 129.32, 128.21, 87.77, 69.20, 44.70, 27.96; Anal. Calcd for $C_{14}H_{18}N_2O_6S$ (342.37): C 49.12, H 5.30, N 8.18. Found: C 49.09, H 5.45, N 8.13.

*4.4.4. 1-(tert-butyl)-2-benzyl azodicarboxylate (**5d**)*

Orange oil (1.31 g, 98.5%). ^{1}H NMR (500 MHz, CD_3Cl) δ 7.43-7.38 (m, 5H, ArH), 5.42 (s, 2H, CH_2), 1.60 (s, 9H, CH_3); ^{13}C NMR (500 MHz, CD_3Cl) δ 160.63, 159.16, 133.89, 129.41, 129.06, 129.02, 87.39, 70.86, 27.94; Anal. Calcd for $C_{13}H_{16}N_2O_4$ (264.28): C 59.08, H 6.10, N 10.60. Found: C 58.98, H 6.14, N 10.55.

*4.4.5. 1-(tert-butyl)-2-(4-methoxybenzyl) azodicarboxylate (**5e**)*

Pale orange solid (1.45 g, 98.6%). Mp 31.2-31.9□. ^{1}H NMR (500 MHz, CD_3Cl) δ 7.38 (d, *J*=8.5Hz, 2H), 6.91 (d, *J*=8.5Hz, 2H), 5.37 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 1.60 (s, 9H, CH_3); ^{13}C NMR (500MHz, CD_3Cl) δ 160.68, 160.56, 159.18, 131.11, 125.97, 114.36, 87.32, 70.87, 55.51, 27.91; Anal. Calcd for $C_{14}H_{18}N_2O_5$ (294.30): C 57.14, H 6.16, N 9.52. Found: C 56.91, H 6.08, N 9.57.

4.5 General procedure for Mitsunobu reactions

A solution of azo-reagent (1.2 mmol,) in THF or CH_2Cl_2 (3 mL) was added slowly to the solution of alcohol (1 mmol), acidic pronucleophile (1.2 mmol) and Ph_3P (1.2 mmol) in THF or CH_2Cl_2 (5 mL) at 0-5□ and the reaction mixture was continued stirring at room temperature. The reaction was monitored by TLC. The solution was concentratred and the toluene was added. The 1-(*tert*-butyl) 2- (4-chlorobenzyl) hydrazinedicarboxylate (**4a**) precipitated and was filtered off. Then the filtrate was evaporated under reduced pressure. The product was purified by column chromatography on silica gel to afford the pure products.

4.5.1. (R)-1-phenylethyl acetate (Entry 1)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=40:1 afforded title compound as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H, ArH), 5.878 (q, *J*=6.5Hz, 1H, CH), 2.06 (s, 3H, CO_2CH_3), 1.53 (d, *J*= 6.5Hz, 3H, CH_3); ^{13}C NMR (500MHz, $CDCl_3$) δ 170.50, 141.86, 128.68, 128.05, 126.27, 72.50, 22.41, 21.54.

4.5.2. benzyl benzoate (Entry 2)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=10:1 afforded title compound as colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.03-8.01 (m, 2H), 7.69-7.66 (m, 1H), 7.56-7.53 (m, 2H), 7.50-7.48 (m, 2H), 7.43- 7.40 (m, 2H), 7.38-7.35 (m, 1H), 5.37 (s, 2H, CH_2); ^{13}C NMR (500MHz, DMSO-d_6) δ 165.80, 136.36, 133.66, 129.82, 129.45, 129.04, 128.76, 128.35, 128.21, 66.41.

4.5.3. (R)-1-phenylethyl benzoate (Entry 3)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=15:1 afforded title compound as colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05-8.03 (m, 2H), 7.69-7.66 (m, 1H), 7.56-7.53 (m, 2H), 7.50-7.48 (m, 2H), 7.41- 7.38 (m, 2H), 7.36-7.31 (m, 1H), 6.08 (q, *J*=6.5Hz, 1H, CH), 1.62 (d, *J*=6.5Hz, 3H, CH_3); ^{13}C NMR (500MHz, DMSO-d_6) δ 165.40, 142.22, 133.84, 130.33, 129.65, 129.24, 128.97, 128.26, 126.29, 73.01, 22.80.

4.5.4. 1-octyl benzoate (Entry 4)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=10:1 afforded title compound as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.04 (m, 2H), 7.56-7.53 (m, 1H), 7.45-7.42 (m, 2H), 4.31 (t, *J*=6.0Hz, 2H, CH_2), 1.80-1.74 (m, 2H, CH_2), 1.46-1.28 (m, 10H, $(CH_2)_5$), 0.88 (t, *J*=7.0Hz, 3H, CH_3); ^{13}C NMR (500MHz, $CDCl_3$) δ 166.69, 132.78, 130.56, 129.54, 128.32, 65.16, 31.82, 29.28, 29.23, 28.76, 26.08, 22.68, 14.12.

4.5.5. 1-(benzyloxy)-4-nitrobenzene (Entry 5)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=15:1 afforded title compound as white solid. Mp 106.3-107.1□. ^{1}H NMR (500 MHz, DMSO-d_6) δ

8.24-8.21 (m, 2H), 7.48 (d, *J*=7.5Hz, 2H), 7.42 (t, *J*=7.5Hz, 2H), 7.38-7.35 (m, 1H), 7.25-7.22 (m, 2H), 5.27 (s, 2H, CH_2); ^{13}C NMR (500MHz, DMSO-d_6) δ 164.10, 141.41, 136.43, 129.03, 128.69, 128.40, 126.35, 115.82, 70.64.

4.5.6. 1-nitro-4-(octyloxy)benzene (Entry 6)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=5:1 afforded title compound as yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.20-8.17 (m, 2H), 6.95-6.93 (m, 2H), 4.04 (t, *J*=6.5Hz, 2H, CH_2), 1.85-1.79 (m, 2H, CH_2), 1.49-1.29 (m, 10H, $(CH_2)_5$), 0.89 (t, *J*=6.0Hz, 3H, CH_3); ^{13}C NMR (500MHz, $CDCl_3$) δ 164.46, 141.46, 126.08, 114.58, 69.10, 31.99, 29.48, 29.41, 29.18, 26.12, 22.86, 14.30.

4.5.7. N-benzylphthalimide (Entry 7)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=10:1 afforded title compound as white solid. Mp 115.5-115.9□. ^1H NMR (500 MHz, $CDCl_3$) δ 8.06-8.04 (m, 2H), 7.56-7.53 (m, 1H), 7.45-7.42 (m, 2H), 4.31 (t, *J*=6.0Hz, 2H, CH_2), 1.80-1.74 (m, 2H, CH_2), 1.46-1.28 (m, 10H, $(CH_2)_5$), 0.88 (t, *J*=7.0Hz, 3H, CH_3); ^{13}C NMR (500MHz, $CDCl_3$) δ 166.69, 132.78, 130.56, 129.54, 128.32, 65.16, 31.82, 29.28, 29.23, 28.76, 26.08, 22.68, 14.12.

4.5.8. N-octylphthalimide (Entry 8)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=10:1 afforded title compound as white solid. Mp 50.5-50.9□. ^1H NMR (500 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H), 7.72-7.70 (m, 2H), 3.68 (t, *J*=7.5Hz, 2H, CH_2), 1.70-1.64 (m, 2H, CH_2), 1.33-1.25 (m, 10H, $(CH_2)_5$), 0.87 (t, J=7.0Hz, 3H, CH_3); ^{13}C NMR (500MHz, $CDCl_3$) δ 168.43, 133.80, 132.18, 123.12, 38.07, 31.77, 29.16, 29.16, 28.61, 26.87 22.62, 14.08.

4.5.9. 2-((4-methoxybenzyl) thio)benzothiazole (Entry 9)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=30:1 afforded title compound as white solid. Mp 69.4-70.1□. ^1H NMR (500 MHz, DMSO-d_6) δ 7.90 (d, *J*=8.0Hz, 1H), 7.50 (d, *J*=7.5Hz, 1H), 7.44-7.41 (m, 1H), 7.37 (d, *J*=8.5Hz, 2H) 7.31-7.28 (m, 1H), 6.87-6.85 (m, 2H), 4.56 (s, 2H, $ArCH_2$), 3.79 (s, 3H, OCH_3); ^{13}C NMR (500MHz, DMSO-d_6) δ 166.48, 158.96, 152.87, 134.88, 130.59, 128.36, 126.60, 124.70, 122.01, 121.40, 114.21, 55.30, 36.51.

4.5.10. N,N-dibenzyl-4-methylbenzenesulfonamide (Entry 10)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=7:1 afforded title compound as white solid. Mp 75.4-76.1□. ^1H NMR (500 MHz, DMSO-d_6) δ 7.78 (d, *J*=8.5Hz, 2H), 7.43 (d, *J*=8Hz, 2H), 7.22-7.20 (m, 5H), 7.08-7.07 (m, 4H), 4.27 (s, 4H, CH_2), 2.42 (s, 3H, CH_3); ^{13}C NMR (500MHz, DMSO-d_6) δ 143.27, 136.54, 136.17, 129.84, 128.15, 128.12, 127.30, 127.02, 51.18, 20.98.

4.5.11. N-benzyloxyphthalimide (Entry 11)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=5:1 afforded title compound as white solid. Mp 143.9-144.7□. ^1H NMR (500 MHz, DMSO-d_6) δ 7.86 (s, 4H), 7.54-7.52 (m, 2H), 7.44-7.41 (m, 2H), 5.18 (s, 2H, CH_2); ^{13}C NMR (500MHz, DMSO-d_6) δ 163.05, 134.75, 134.11, 129.60, 129.05, 128.46, 128.41, 123.20, 79.18.

4.5.12. N-octyloxyphthalimide (Entry 12)

Following the general procedure: Flash chromatography eluted with Petroleum ether/ EtOAc=5:1 afforded title compound as pale yellow solid. Mp 34.5-34.9□. ^1H NMR (500 MHz, $CDCl_3$) δ 7.85-7.82 (m, 2H), 7.78-7.74 (m, 2H), 4.203 (t, *J*=7Hz, 2H, OCH_2), 1.82-1.76 (m, 2H, CH_2), 1.51-1.45 (m, 2H, CH_2), 1.38-1.25 (m, 8H, $(CH_2)_4$), 0.88 (t, *J*=7Hz, 3H, CH_3); ^{13}C NMR (500MHz, $CDCl_3$) δ 163.84, 134.61, 129.17, 123.64, 78.82, 31.96, 29.47, 29.34, 28.35, 25.74, 22.83, 14.29.

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