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Stereoselective Construction of Highly Functionalized Azetidines via a [2 + 2]-Cycloaddition

Yang Ye, Hua Wang, and Renhua Fan*

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China, and Shanghai Key Laboratory of Molecular Catalysts and Innovative Materials, Department of Chemistry, Fudan University, Shanghai 200433, China

rhfan@fudan.edu.cn

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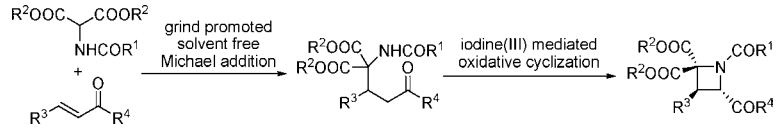
ABSTRACT



A facile stereoselective synthesis of highly functionalized azetidines from a novel [2 + 2]-cycloaddition of 2-aminomalonates to chalcones is reported. The desired four-membered ring construction proceeded via a grind-promoted solvent-free Michael addition and a PhIO/Bu_4NI mediated oxidative cyclization and afforded azetidines in moderate to good yields with excellent diastereoselectivities.

Azetidines constitute a very important class of compounds because of their remarkable medicinal and biological activities.[1,2] For example, the natural products mugineic acid,[3a] nicotianamine,[3b] polyoxins,[3c] and trombin inhibitor melagatran[3d] have an azetidine carboxylic acid unit as their core structure. As constrained four-membered azacycles, azetidines could undergo various transformations to afford a wide variety of nitrogen-containing compounds.[4] Recently, azetidines have been utilized as efficient chiral ligands for asymmetric syntheses as a result of their rigid scaffold.[5] Intramolecular nucleophilic substitution (including Mitsunobu-type reaction) of 1,3-amino halide or 1,3-amino

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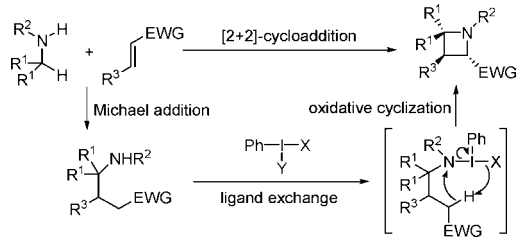
alcohol derivatives is the classical and commonly used approach to azetidines.[6] Numerous efforts have been made to synthesize azetidine derivatives with higher efficiency. The Tanaka group reported the synthesis of alkenylazetidines from the palladium-catalyzed cyclization of *N*-arylsulfonyl-α-amino allenes.[7] The Tunge group found a palladium-catalyzed decarboxylative ring contraction of 6-vinyl oxazinanones to form vinyl azetidines.[8] Kise and co-workers developed an electroreduction of chiral aromatic imino esters to synthesize *cis*-2,4-disubstituted azetidine-3-ones.[9] Also, the De Kimpe group described a rearrangement of *β*,*γ*-aziridino α-amino esters to prepare 3-aminoazetidine-2-carboxylic esters.[10] Alternatively, oxidative cyclization can directly convert C−H bonds into C−C or C−X bonds to yield cyclic compounds efficiently without extra chemical transformations.[11] Recently, we have directed our focus to the synthesis of cyclopropane,[12a] oxetane,[12b] and dihydrofuran derivatives[12c] via iodine(III)-mediated[13] oxidative cyclizations. In order to further extend the utility of this approach, we investigated the possibility of constructing highly functionalized azetidines via a novel [2 + 2]-cycloaddition process involving a Michael addition and iodine(III)-mediated oxidative cyclization (Scheme 1).

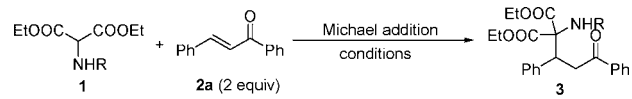
Scheme 1



First, we studied the Michael additions of diethyl 2-aminomalonates **1a**−**1f** with chalcone **2a** (Table 1). The preliminary survey was carried out in DMSO in the presence of K_2CO_3 at 25 °C. Only reactions with *N*-Boc- and *N*-Bz-2-aminomalonates afforded the corresponding Michael adducts in very low yields (Table 1, entries 1−6). Unfortunately, further efforts to optimize reaction conditions by varying solvents (Table 1, entries 7−11), base, additive, and temperature fail to improve the product yield beyond 30%. However, performing the reaction under a grinding operation without solvent with the introduction of a phase transfer catalyst ($PhEt_3NCl$) dramatically improved the yield of Michael adduct **3e** to 90% (Table 1, entry 12). As control experiments, the reaction performed using a regular magnetic stir procedure did not afford any product. Replacements of $PhEt_3NCl$ by Bu_4NX (X = Cl, Br, I) resulted in much lower yields of product **3e** (Table 1, entries 13−16).

We next investigated the oxidative cyclization of the Michael adduct **3e** using the combination of PhIO and Bu_4NI. An experiment was carried out to employ optimized conditions [PhIO (2.0 equiv), Bu_4NI (1.2 equiv), toluene, 25 °C, 12 h], with which diethyl 1,4-dibenzoyl-3-phenylazetidine-2,2-dicarboxylate **4ea** was formed in 76% yield (Scheme 2). The relative stereochemistry of **4ea** was determined on the basis of its ^1H NMR and single-crystal diffraction analysis. Oxidative cyclization could also proceed smoothly in water

Table 1. Evaluation of Conditions for Michael Addition of 2-Aminomalonates with Chalcone

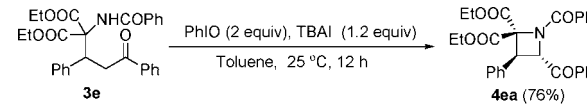


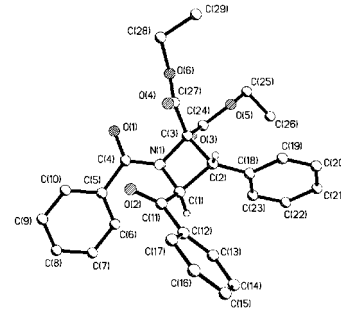
1a: R = H
1b: R = CH_3
1c: R = $COCH_3$
1d: R = Boc
1e: R = COPh
1f: R = Ts

entry	1	conditions (equiv)[a]	3 (yield, %)[b]
1	**1a**	DMSO, K_2CO_3 (1), 12 h	**3a** (0)
2	**1b**	DMSO, K_2CO_3 (1), 12 h	**3b** (0)
3	**1c**	DMSO, K_2CO_3 (1), 12 h	**3c** (0)
4	**1d**	DMSO, K_2CO_3 (1), 12 h	**3d** (5)
5	**1e**	DMSO, K_2CO_3 (1), 12 h	**3e** (6)
6	**1f**	DMSO, K_2CO_3 (1), 12 h	**3f** (0)
7	**1e**	Toluene, K_2CO_3 (1), 12 h	**3e** (0)
8	**1e**	$ClCH_2CH_2Cl$, K_2CO_3 (1), 12 h	**3e** (0)
9	**1e**	EtOAc, K_2CO_3 (1), 12 h	**3e** (6)
10	**1e**	THF, K_2CO_3 (1), 12 h	**3e** (26)
11	**1e**	MeOH, K_2CO_3 (1), 12 h	**3e** (29)
12	**1e**	neat, K_2CO_3 (1), $PhEt_3NCl$ (1), 10 min, grind	**3e** (90)
13	**1e**	neat, K_2CO_3 (1), $PhEt_3NCl$ (1), 12 h	**3e** (0)
14	**1e**	neat, K_2CO_3 (1), Bu_4NCl (1), 10 min, grind	**3e** (3)
15	**1e**	neat, K_2CO_3 (1), Bu_4NBr (1), 10 min, grind	**3e** (9)
16	**1e**	neat, K_2CO_3 (1), Bu_4NI (1), 10 min, grind	**3e** (17)

[a] Reaction conditions: substrate **1** (0.2 mmol), **2a** (0.4 mmol), K_2CO_3 (0.2 mmol), and solvent (1 mL) at 25 °C, unless noted. [b] Isolated yield based on substrate **1**.

Scheme 2. Oxidative Cyclization of Michael Adduct **3e** and X-ray Diffraction Structure of Azetidine **4ea**

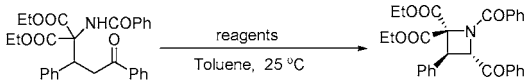




and afforded the product in 65% yield, albeit in a longer reaction time (48 h).

Several control experiments were conducted to specify the reaction pathway (Scheme 3). Bu_4NBr was also an effective

Scheme 3. Control Experiments for the Oxidative Cyclization

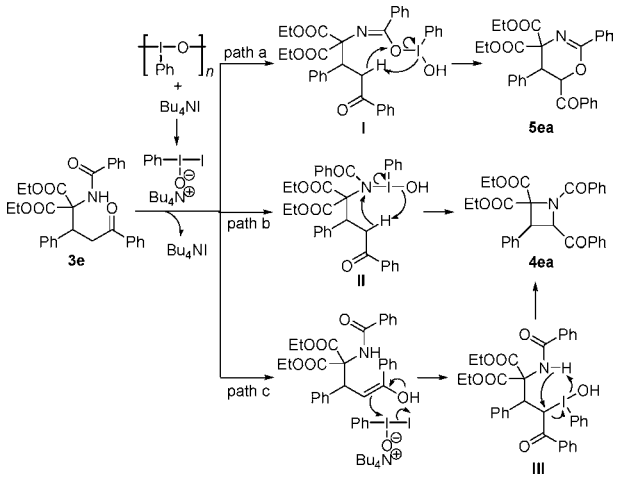


reagents	**4ea** yield
PhIO (2 equiv), Bu_4NBr (1.2 equiv)	64%
PhIO (2 equiv), Bu_4NCl (1.2 equiv)	0%
$PhI(OAc)_2$ (2 equiv), Bu_4NI (1.2 equiv)	0%
PhIO (2 equiv), LiI (1.2 equiv)	0%
PhIO (2 equiv), NaI (1.2 equiv)	0%
PhIO (2 equiv), KI (1.2 equiv)	0%
PhIO (2 equiv), Bu_4NI (0.2 equiv)	18%
PhIO (2 equiv), Bu_4NI (0.2 equiv), KI (1 equiv)	21%
I_2 (2 equiv), Bu_4NOH (1.2 equiv)	0%

reagent, whereas the reaction with Bu_4NCl did not yield the expected azetidine. When PhIO was replaced by $PhI(OAc)_2$, no reaction was observed. Tetrabutylammonium cation was important because the experiments with LiI, NaI, and KI failed to achieve oxidative cyclization. To exclude the possibility that the reaction was mediated by I_2, Michael adduct **3e** was treated with a combination of I_2 and Bu_4NOH, and no azetidine was formed.

According to the above results and our previous reports,[12] a reaction pathway can be presumed as shown in Scheme 4.

Scheme 4. Mechanistic Hypothesis for the PhIO/Bu_4NI Mediated Oxidative Cyclization



The depolymerization of iodosobenzene by tetrabutylammonium iodide (or bromide) generates a new iodine(III) species,[14] which has a higher reactivity in the ligand exchange reaction due to its basicity and the good leaving ability of iodide. Michael adduct **3e** reacts with this iodine(III) species via a ligand exchange to form intermediate **II**, which is ready to undergo an intramolecular reductive elimination to afford the expected azetidine **4ea** (path b). An alternative pathway for the formation of azetidine involves an α hyperiodination of the methylene of the phenyl ketone in compound **3e** followed by an intramolecular attack by the nitrogen atom to yield azetidine accompanied by the reductive elimination of PhI (path c). In our experiments, no dihydro-1,3-oxazine **5ea** was isolated. This result indicates that the iodine(III)-mediated four-membered oxidative cyclization is much more favorable than six-membered oxidative cyclization (path a).

In an attempt to make this approach more efficient, a one-pot [2 + 2]-cycloaddition was tested, and 56% isolated yield of azetidine was obtained. Unconsumed base from the Michael addition step resulted in the decomposition of Michael adduct **3e** and azetidine **4ea**. When a workup procedure for the Michael addition mixture was introduced, the yield of **4ea** over two steps increased to 65%, and no further purification for Michael adduct was required. It is noteworthy that the reaction was carried out in an open-air system, with no extra protective atmosphere required. The scope of this [2 + 2]-cycloaddition for the synthesis of highly functionalized azetidines was demonstrated to be a quite general synthetic approach (Scheme 5). For most cases, 2-aminomalonates **1** reacted with chalcones **2** leading to the corresponding products **4** in moderate to good yields. Additionally, the reaction was found to tolerate a range of

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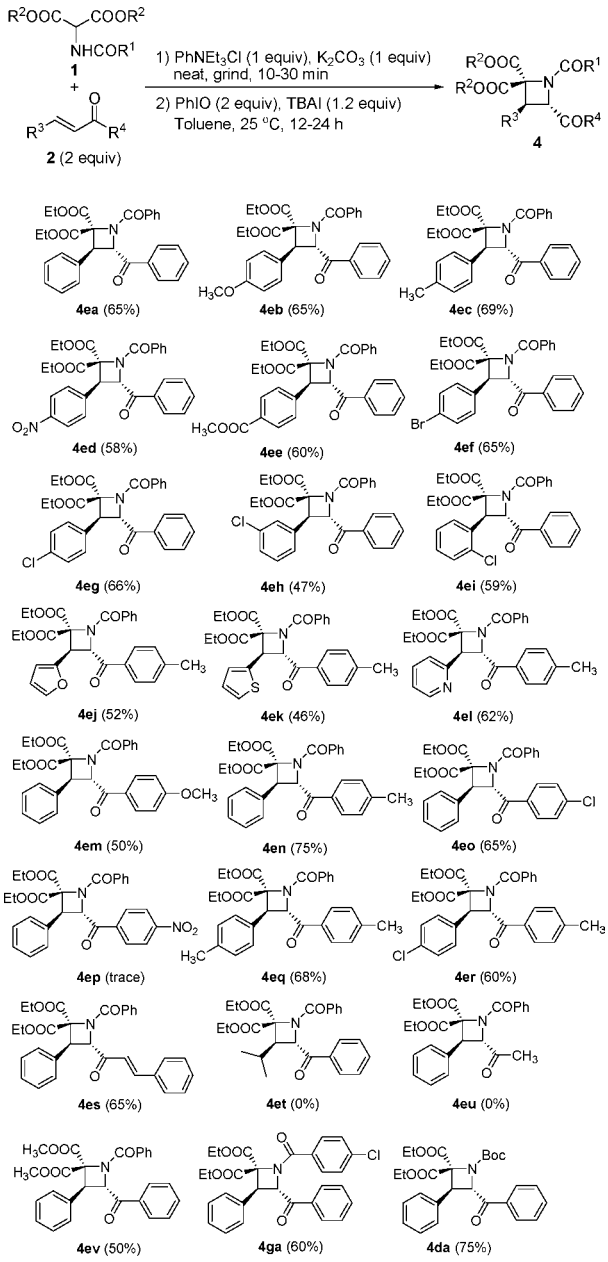
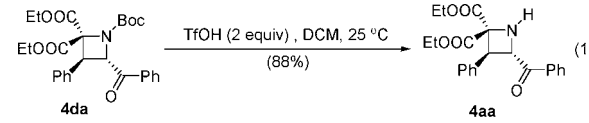
Scheme 5. [2 + 2]-Cycloaddition To Construct Highly Functionalized Azetidines



different groups with different electronic demands on the R^3 aromatic ring. Heterocycle substituted azetidines **4ej**, **4ek**, and **4el** could also be efficiently constructed. An electronic substrate effect was observed on the R^4 group of chalcones. Reactions of *p*-CH_3- or *p*-Cl-substituted chalcone **2n** or **2o** afforded azetidine **4en** or **4eo** in 75% or 65% yield, respectively. A stronger electron-donating substitution (*p*-CH_3O-) on the R^4 aromatic ring (chalcone **2 m)** led to a lower reactivity during the Michael addition step and a lower yield of azetidine **4em**, whereas a stronger electron-withdrawing substitution (*p*-NO_2-) resulted in the failure in the oxidative cyclization step to form azetidine **4ep**. 1,5-Diphenylpenta-1,4-dien-3-one **2s** was also found to be a suitable substrate for [2 + 2]-cycloaddition with *N*-Bz-2-aminomalonate. Aliphatic substrates **2t** and **2u** were unreactive under the same Michael addition conditions. With respect to other 2-aminomalonates, *N*-*p*-Cl-C_6H_4CO- and *N*-Boc-2-aminomalonates **1g** and **1d** were suitable partners in this process and the desired products **4ga** and **4da** were isolated in good yields.

The treatment of *N*-Boc azetidine **4da** with trifluoromethanesulfonic acid gave rise to azetidine **4aa** in 88% yield (eq 1). All azetidines were formed with a high diastereoselectivity (*anti*:*syn* >95:5, determined by ^{1}H NMR).



In conclusion, we have developed an efficient stereoselective synthesis of highly functionalized azetidines from a [2 + 2]-cycloaddition of 2-aminomalonates with chalcones via a grind-promoted, solvent-free Michael addition and a PhIO/Bu_4NI mediated oxidative cyclization. The desired four-membered ring construction proceeds under mild conditions with good functional group tolerance. The current direction for future research is aimed at extending the scope and potential synthesis applications, as well as investigation of asymmetric transformations.

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Supporting Information Available: Experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR of new compounds, and crystallographic data of compound **4ea** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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