Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201300810

# Catalytic Oxidation of C($sp^3$)–H Bonds Induced by a Radical Cation Salt: Construction of 1,4-Dihydropyridines Using a Fragment-Reassembly Strategy

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Received: September 5, 2013; Revised: January 14, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300810.

**Abstract:** A fragment-reassembly strategy was applied to the construction of 1,4-dihydropyridines and phosphorus-substituted 1,4-dihydropyridines under catalytic radical cation salt-induced C($sp$)$^3$–H functionalization of glycine derivatives. Mechanistic studies show that domino C(sp)$^3$–H bond oxidation and C–N bond cleavage reactions are involved.

**Keywords:** C–H oxidation; C–N cleavage; 1,4-dihydropyridines; fragment-reassembly strategy; radical cation salts

The substitution reaction, where a leaving group is substituted by a nucleophile to construct a new C–C or C–X bond is fundamental in chemistry. Generally, a leaving group such as a halide or pseudohalide possessing a polarized and labile bond to the site of nucleophilic attack is essential to a successful substitution reaction [Figure 1, Eq. (1)]. Conversely, amines have been virtually overlooked as leaving groups, despite the numerous examples of their use as nucleophiles in substitution reactions.[1] The relatively high stability of the respective C–N bond, contrasts some of the desired characteristics of a good leaving group. It is for this reason that examples of amine leaving groups are limited in the literature. More importantly, the few reported uses have resulted in the permanent loss of the N-leaving group to stoichiometric waste [Figure 1, Eq. (2)]. Mindful of these limitations, we were interested in designing a methodology to expand the scope of amine leaving groups, while addressing the critical issue of nitrogen loss. We questioned whether the amino group of the starting material, which initially acts as a leaving group, could be trapped by an active functional group after it is expelled from the parent substrate [Figure 1, Eq. (3)]. We sought to test this hypothesis in the synthesis of 1,4-dihydropyridines (1,4-DHP) (Figure 2). This

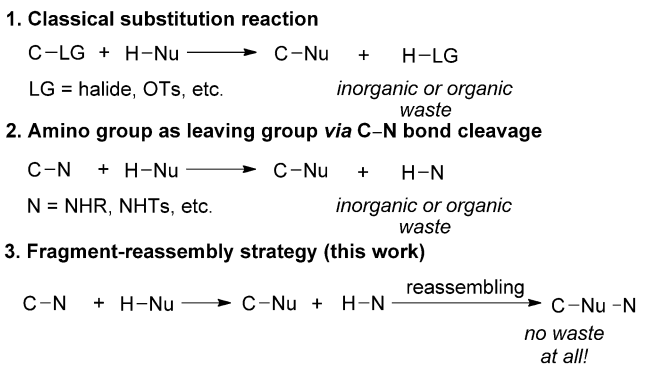


**Figure 1.** Normal substitution reactions *vs.* fragment-reassembly strategy.

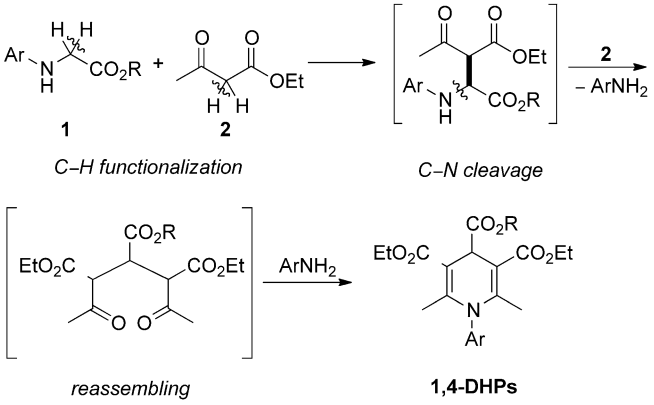


**Figure 2.** Construction of 1,4-DHPs by the fragment-reassembly strategy.

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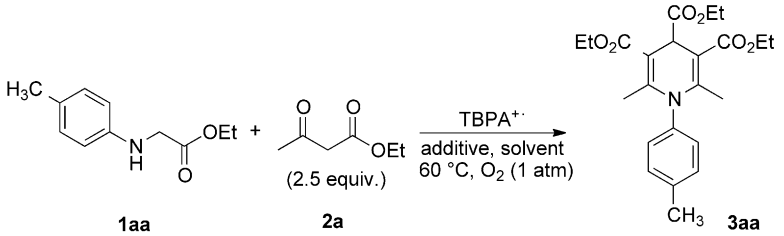
**Table 1.** Optimization of the reaction conditions.




1aa 2a 3aa

| Entry | Solvent | $TBPA^{+\cdot}$ (mol%) | Additive (10 mol%) | Time [h] | Yield[a] [%] |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 5 | $InCl_3$ | 24 | 38 |
| 2 | $CH_3CN$ | 10 | $InCl_3$ | 2.5 | 55 |
| 3 | $CH_3CN$ | 20 | $InCl_3$ | 2.5 | 57 |
| 4 | $CH_2Cl_2$ | 10 | $InCl_3$ | 24 | $<10$ |
| 5 | $CHCl_3$ | 10 | $InCl_3$ | 24 | $<5$ |
| 6 | THF | 10 | $InCl_3$ | 24 | trace |
| 7 | MeOH | 10 | $InCl_3$ | 24 | 51 |
| 8 | EtOH | 10 | $InCl_3$ | 24 | 30 |
| 9 | $CH_3CN$ | 10 | $FeCl_2$ | 20 | 10 |
| 10 | $CH_3CN$ | 10 | $BF_3{\cdot}Et_2O$ | 12 | 42 |
| 11 | $CH_3CN$ | 10 | $FeCl_3$ | 12 | 60 |
| 12 | $CH_3CN$ | 10 | CuI | 12 | 56 |
| 13 | $CH_3CN$ | 10 | $CuBr_2$ | 12 | 57 |
| 14 | $CH_3CN$ | 10 | CuCl | 12 | 40 |
| 15 | $CH_3CN$ | 10 | CuBr | 1.5 | 47 |
| 16 | $CH_3CN$ | 10 | CAN | 24 | 34 |
| 17 | $CH_3CN$ | 10 | $Mn(OAc)_3$ | 24 | 25 |

[a] *Reaction conditions:* glycine ester **1aa** (0.5 mmol), 1,3-dicarbonyl compound **2a** (1.25 mmol), $TBPA^{+\cdot}$ (10 mol%), additive (10 mol%), 5 mL solvent, 60 °C, under 1 atm $O_2$; all yields are of isolated products.

atom-economic approach would represent an interesting example of nitrogen being used as an incorporable leaving group. If this fragment-reassembly strategy would be feasible, it could be of high synthetic importance as it could inspire new synthetic disconnections in heterocycle synthesis.

1,4-DHPs are an important class of drugs for the treatment of cardiovascular diseases. One example being nitrendipine, which is a DHP calcium channel blocker and is used in the treatment of primary hypertension to decrease blood pressure.[2] Hantzsch 1,4-dihydropyridine derivatives are regarded as models of coenzyme NADH to investigate the biological hydride transfer mechanism.[3] Hantzsch esters also are widely used as hydride donors in catalytic hydrogenation including asymmetric variants.[4,5] Until now, the synthesis of Hantzsch 1,4-DHP derivatives is mainly confined to the classical Hantzsch reaction as well as some limited approaches.[6] Thus, more efficient and convenient synthetic methods which allow access to these derivatives are a worthwhile endeavour.

Recently, we reported, for the first time, the catalytic radical cation-initiated C–H functionalization of glycine derivatives with styrenes to build quinoline skeletons both inter- and intramolecularly.[7] This method represented a novel approach to CDCs (cross dehydrogenative coupling reactions), avoiding using excess quantities of the oxidants (such as DDQ, TEMPO, oxoammonium, and peroxides).[8] This methodology was also applied to the catalytic aromatization of 1,4-dihydropyridines.[9] When other nucleophiles (indoles, for example) were used to trap the *in situ* generated radical intermediate, C–N cleavage occurred, producing the corresponding aniline by-products.[10] If 1,3-dicarbonyls were employed, the leaving anilines would further react with the 1,5-dicarbonyl intermediate to form 1,4-dihydropyridines (Figure 2).[11] To test the possibility of this fragment-reassembling strategy, the reaction between glycine ester and ethyl acetoacetate was employed under catalytic radical cation salt-induced conditions. To our great delight, the reaction occurred smoothly, producing the desired 1,4-dihydropyridines in moderate yield. Herein, we wish to report a novel method for the direct functionalization of $C(sp^3)$–H bonds of glycine derivatives using the fragment-reassembly strategy, to construct 1,4-dihydropyridines.

We began our study with reaction of glycine ester (**1aa**) with ethyl acetoacetate (**2a**) in the presence of $TBPA^{+\cdot}$ [tris(4-bromophenyl)aminium hexachloroantimonate] (Table 1). In the presence of 5 mol% of $TBPA^{+\cdot}$ and 10 mol% $InCl_3$ under $O_2$ (1 atm), the re-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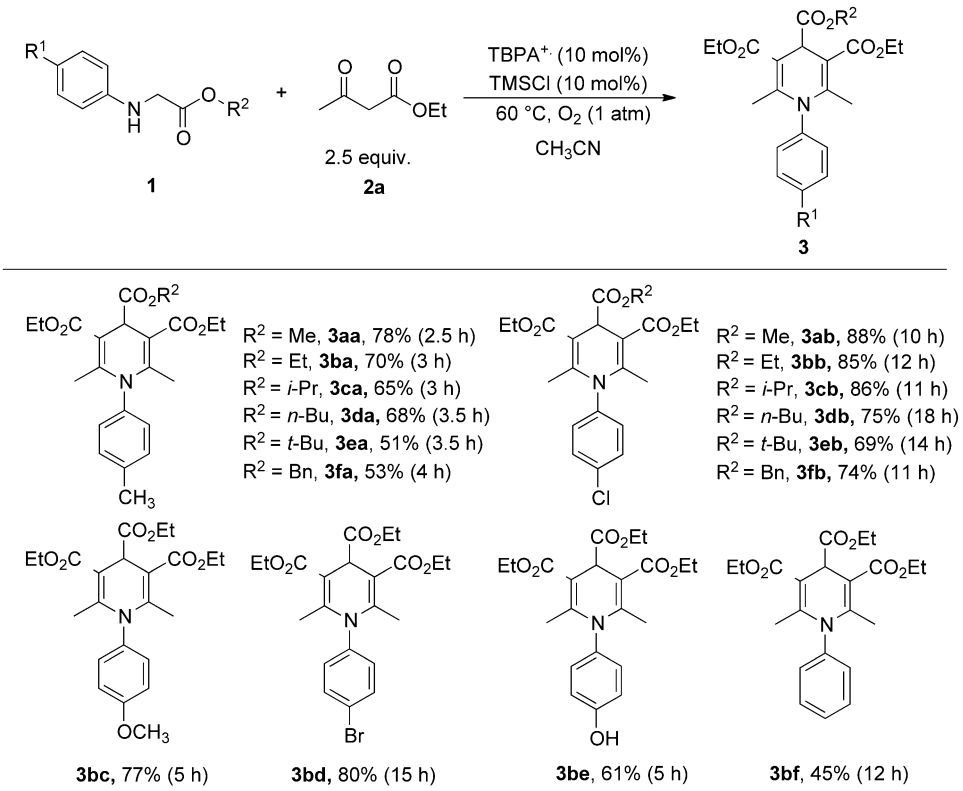


**Scheme 1.** The reactions between glycine derivatives and ethyl acetoacetate. All yields are of isolated products.

action gave a moderate yield of the desired product **3aa** (entry 1).[12] When 10 mol% of $TBPA^{+\cdot}$ was added, the yield was increased to 55% (entry 2). Higher catalyst loading did not improve the yield significantly (entry 3). A solvent screening was then performed, and $CH_3CN$ was the best solvent while $CHCl_3$, $CH_2Cl_2$, THF, MeOH and EtOH all resulted in lower yields of the desired product (entries 4–8). To further improve the yield, different additives were tested (entries 9–16). $FeCl_2$ showed a deleterious effect to the reaction and decreased the yield dramatically (entry 9). $BF_3{\cdot}Et_2O$ also did not exhibit a positive effect on the formation of the desired product (entry 10). Comparable results were obtained when $FeCl_3$, CuI, $CuBr_2$, CuCl and CuBr added (entries 11–15), which implied that the activation of **2a** might be more important than **1aa** in this reaction. Other oxidants were then tested, but the efficiency of the reaction decreased dramatically, providing the desired product in 34% and 25% yields, respectively (entries 16 and 17). These results showed that $TBPA^{+\cdot}$ is better than other oxidants. So TMSCl was added to accelerate the enolization of ethyl acetoacetate. To our delight, the best result obtained in the presence of 10 mol% TMSCl and the 1,4-dihydropyridine was isolated in 78% yield (entry 18).

With the optimized conditions in hand, we employed various glycine esters with ethyl acetoacetate to test this reaction's generality. Firstly, 4-methylanilino-substituted glycine esters were chosen as model substrates with electron-donating groups to test the efficiency of the reaction. A slight steric effect was observed when the substituents were present on the esters, such as **3aa** compared with **3ea** (Scheme 1, **3aa**–**3fa**). Benzyl-substituted ester also decreased the yield to 53%, probably due to the existence of another active benzyl C($sp^3$)–H bond in the molecule, which might disturb the oxidation process. Then, 4-chloroaniline-substituted substrates as model compounds with electron-withdrawing groups were employed under the standard conditions. As a whole, EWGs increase the difficulty of the C–H bond oxidation and prolonged reaction times were required to achieve full conversion of the starting materials (Scheme 1, **3ab** to **3fb**). However, higher yields were obtained compared to substrates with EDGs. This is accredited to the electron-donating groups making the substrate more easily oxidized, resulting in some by-product (observed by crude $^1H$ NMR) formation by uncontrolled oxidation. The reactions of methoxy- and bromo-substituted glycine esters could also occur smoothly, affording good yields of the 1,4-dihydropyridine products (Scheme 1, **3bc** to **3bd**). It is worth noting that a free phenolic hydroxy group could also be tolerated, producing the desired product in good yield (**3be**), which avoided hydroxy group protection

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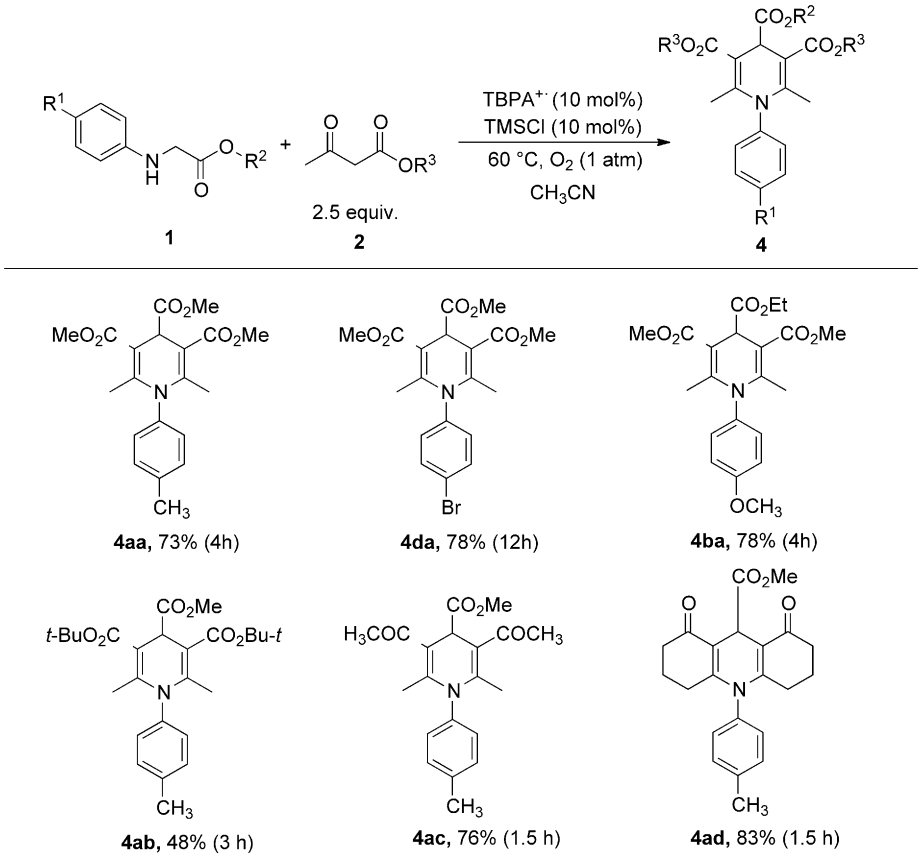


**Scheme 2.** The reactions between glycines and 1,3-dicarbonyls. All yields are of isolated products.

in further functionalizations. In the absence of a *para*-substituent at the aniline, the 1,4-dihydropyridines were isolated in lower yields (**3bf**). The main reasons probably lie in the fact that when the substrate was oxidized, coupling on the *para*-position of the aniline section would occur.[13]

Having demonstrated the scope of glycine ester **1** in the fragment-reassembly reaction of **2a**, we wanted to explore the scope further by employing other 1,3-dicarbonyl compounds.[14] The results show that not only β-keto esters, but also 1,3-diketones reacted with glycine esters to give the desired products in good yields (Scheme 2), in which the structure of **4da** was unambiguously assigned by X-ray crystallographic analysis (Figure 3).[15] Only *tert*-butyl acetoacetate gave a lower yield (**4ab**), presumably due to steric hindrance.

It is well-known that organophosphorus compounds are important substrates in the study of biochemical processes, and amino phosphonates play an important role as enzyme inhibitors, agrochemicals, and pharmaceuticals, due to their structural resemblance to the corresponding amino acids.[16] Azaheterocyclic phosphonates, as an important class of derivatives of amino phosphonates, have been studied intensively for agriculture to medicine purposes.[17]

Given success in the efficient construction of the skeleton of 1,4-dihydropyridines *via* the fragment-reassembly strategy, we decided to apply this methodology to a more challenging target, phosphorus-substituted 1,4-dihydropyridines, whose synthesis was only achieved in limited cases.[18] To our delight, α-anilino phosphonates reacted with 1,3-dicarbonyl compounds smoothly to afford the 4-phosphonylated 1,4-dihydropyridines in good yields (Scheme 3). We believe that

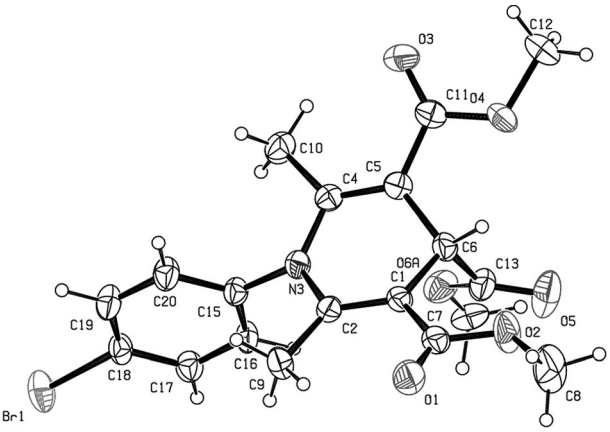


**Figure 3.** ORTEP drawing of product **4da**.


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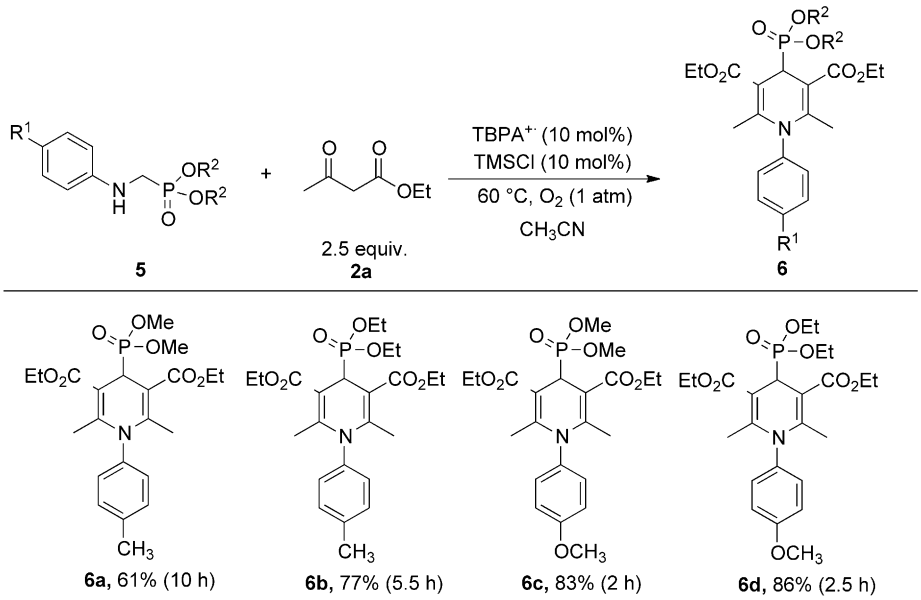
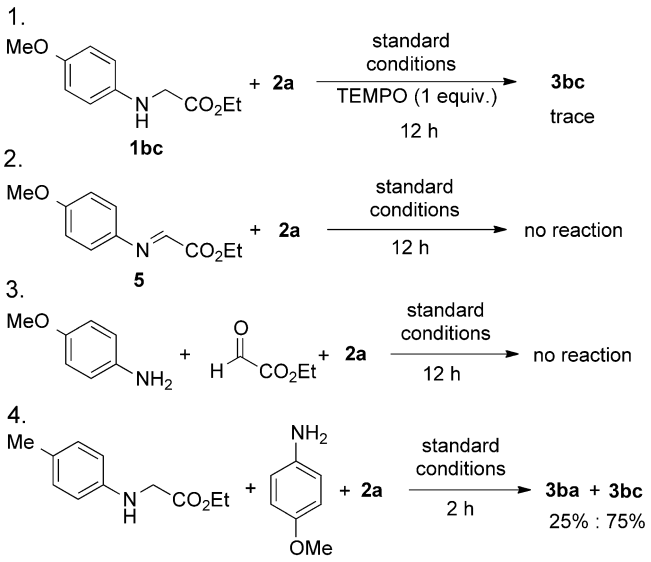



**Scheme 3.** Synthesis of phosphorus 1,4-dihydropyridines *via* the fragment-reassembly strategy. All yields are of isolated products.




**Scheme 4.** Control experiments.

these transformations provide a new way to the synthesis of phosphorous azaheterocycles. Studies on further applications in the construction of this class of azaheterocyclic phosphonates are still underway in this laboratory, and will be reported in due course.

To probe the mechanism of this transformation, several experiments were performed (Scheme 4). The reaction between **1bc** and **2a** was conducted in the presence of 1 equivalent of the radical inhibitor TEMPO and the reactivity was almost fully attenuated and only trace amounts of the desired product was detected, which implied that free radical intermediate was involved in the reaction process [Scheme 4, Eq. (1)]. When the standard reaction conditions were applied to glycine imine **5**, the reaction was messy, and no 1,4-dihydropyridines was detected by $^1$H NMR analysis of the crude reaction mixure. This is caused by the glycine imines being prone to be oxidation. These results show that the reaction proceeded *via* radical addition instead of imine formation (see Scheme 5). A three-component reaction of aniline, ethyl glyoxalate and ethyl acetoacetate was further performed, and only a trace of the 1,4-dihydropyridine was formed, which also partly rules out the formation of imine. To confirm the process of C–N bond cleavage, a competing experiment between *N*-(4-methylphenyl)glycine ester, 4-methoxyaniline and **2a** was conducted. From crude $^1$H NMR analysis we can see that products **3ba** and **3bc** were generated in a ratio of 1:3, which demonstrated that anilines were formed *in situ via* C–N bond cleavage.

Based on the results of control experiments, a plausible mechanism was proposed. Glycine ester was oxidized by TBPA$^{+\cdot}$ in the presence of $O_2$, yielding a radical intermediate **A**, which readily reacted with 1,3-dicarbonyl compounds catalyzed by TMSCl. After oxidation and loss of TMS$^+$, which was regenerated and participated in the next catalytic cycle, an intermediate **B** was generated, and then C–N bond cleavage occurred, in which the aniline group served as a leaving group, producing a 1,5-dicarbonyl intermediate **C**. The leaving aniline further reacted with this 1,5-dicarbonyl intermediate to afford the 1,4-dihydropyridine product. More details of the mechanism are currently under investigation in this laboratory.

In conclusion, we have demonstrated the efficient synthesis of 1,4-dihydropyridines using the fragment-

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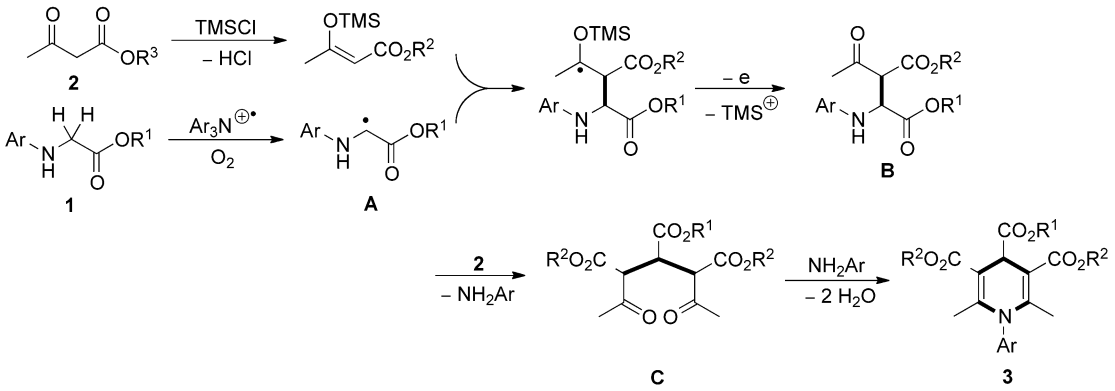


**Scheme 5.** The proposed mechanism.

reassembly strategy proceeding *via* radical cation salt-prompted C($sp^3$)–H oxidation/C–N bond cleavage. The catalytic aerobic oxidation of glycine esters was screened for a broad range of substrates. This approach provides a direct access to biologically relevant 1,4-dihydropyridines in high yields. It is worth highlighting that 4-phosphonylated 1,4-dihydropyridine can also be generated efficiently by this method. The mild reaction conditions, good functional group tolerance and the high efficiency of the oxidative functionalization make the present transformation attractive for future applications. Further studies are in progress in our laboratory.

## Experimental Section

### Typical Procedure

A solution of **1aa** (0.5 mmol), **2a** (1.25 mmol) and TMSCl (10 mol%) in $CH_3CN$ (3 mL) was mixed fully and flushed with $O_2$ (keep flushing until the reaction completed), then the solution of $TBPA^{+\cdot}$ (10 mol%) in $CH_3CN$ (2 mL) was added dropwise. The reaction solution was stirred under 60 °C. After completion as monitored by TLC (2.5 h), the reaction was quenched with sodium carbonate/methanol solution. The mixture was poured into a separatory funnel with the addition of excess DCM, and then the crude organic solution was extracted three times with water to remove inorganic salts. The organic phase was then dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure and the products were separated by basic aluminium oxide column chromatography eluted with petroleum ether/acetone (v/v 20:1) to afford the product **3aa**; yield: 78%.

## Acknowledgements

*We thank Natural Science Foundation of China (NSFC) (No. 21002079 and 21362030) for supporting our research.*

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[12] Although 1,4-DHPs tend to be oxidized, no aromatization product was observed in the standard reaction conditions. We also tried to oxidize the DHPs to pyridines using 1 equivalent of DDQ, but no aromatization product was found. This is probably due to the fact that there are Ar groups on nitrogen of DHPs. If there is no protecting group on nitrogen, aromatization will occur smoothly (see ref.[9]).
[13] See the supporting information of ref.[8f]
[14] We tested the possibility to synthesize unsymmetrical DHPs, using two different 1,3-dicarbonyl compounds, but a mixture of DHPs was isolated. From crude the $^1$H NMR spectrum, the unsymmetrical DHP was the minor product. These results show that the synthesis of unsymmetrical DHPs was still a great problem based on the present method.
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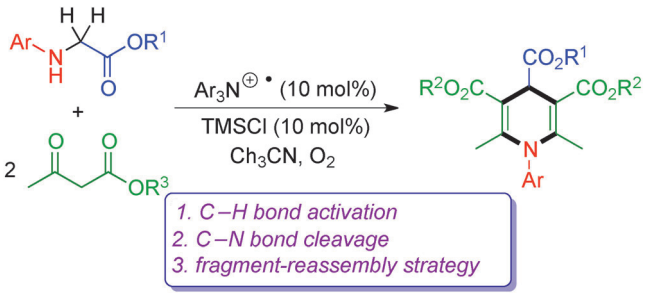


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