



Light promoted aqueous phase amine synthesis via three-component coupling reactions



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ABSTRACT

By applying a simple $\text{TiO}_2\text{-(NH}_4)_2\text{S}_2\text{O}_8$ system and promoted by UV light, the three-component reactions of cyclic ether, aniline and aldehyde can be progressed efficiently. 29 substituted amines with different structures were synthesized with up to 97% isolated yields. Isotope effect study revealed that the rate-determining step might be the nucleophilic addition step but not radical generation.

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The selective C–H bond functionalization is one of the fundamental problems in chemistry.¹ Due to the stability of C–H bond, especially the unactivated sp^3 C–H bond, the pre-functionalization is necessary in order to realize the selective transformation reactions, which results in low atomic efficiency and serious environment pollution. The development of a new catalyst to realize the selective transformation of C–H bond under mild reaction conditions will undoubtedly be interesting in the synthesis of many functional substrates. The application of transition metal catalyst is an efficient method to carry out the C–H bond activation.¹ Normally, the transition metal can react with C–H bond to produce C–M bond and it can be selectively transformed into desired product. In the last years, a variety of catalytic C–H bond activation processes have been developed with excellent performance.

Except the catalytic activation of C–H bond via the formation of C–M bond, the C–H bond activation through the formation of radical is also an attractive route.² Since 1980s the radical chemistry based synthetic methods have been studied extensively, which is strictly related to the development of new radical precursors. Therefore, the discovery of a specific radical initiator for a specific reaction is one of the major tasks for researchers in order to find a valuable synthetic method. In the last decades, many radical initiators such as azo compounds or peroxides,³ samarium iodide,⁴ triethylborane,⁵ hexabutyliditin,⁶ indium⁷ and dimanganese decacarbonyl⁸ have been reported and many good results were obtained. Recently, great progresses have been achieved in the

catalytic addition of RX ,^{7,9} HCONH_2 ,¹⁰ olefins¹¹ and Mitsunobu's reagent¹² to imines. Besides the reactions discussed above, the selective addition of cyclic ethers to C=N bond is one of the challenging reactions in this field. About this transformation,^{13–17} good results were obtained under ionizing radiation¹³ or in the presence of large excess of Me_2Zn ,^{2a,15} $\text{TiCl}_3/\text{PhN}_2$ ⁺¹⁶ or ROOH/PhN_2 ^{+2b,c,17} as radical initiator. Undoubtedly, the usage of large excess of radical initiators is one of the big disadvantages of the radical based synthetic method. It makes the reaction complicated and difficult for the treatment of the reaction. Meanwhile, the generality of the methodology is usually limited and the selectivities to the desired products are not good enough. It would be an ideal choice if a clean, economic and general method can be developed for this transformation. Herein, we would like to present our new results about the light promoted activation of cyclic ether and its application in the three-component coupling reactions with aldehydes and anilines. The reaction was initiated with $\text{TiO}_2\text{-(NH}_4)_2\text{S}_2\text{O}_8$ and promoted by UV-light.

The catalytic performance of this system was first explored using the reaction of *p*-toluidine, benzaldehyde and 1,4-dioxane as model reaction, Table 1. Clearly, the combination of TiO_2 and UV is essential to gain the selective transformation of the three-component reaction. The desired product **3a** was not detectable in the absence of TiO_2 , entry 1. The three-component reaction can progress well if a suitable amount of TiO_2 was added and the selectivity to **3a** increased to 66%, entry 2. The addition of water as co-solvent is indispensable to realize the transformation. Almost no nucleophilic addition product of 1,4-dioxane was observed under water free condition, entry 3. As a radical initiator is extensively used, the applying

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Table 1
Reaction condition optimization^a

Entry	Initiator	Additive	Sel. ^b (%)
1	—	—	0
2	TiO ₂	—	66
3 ^c	TiO ₂	—	3
4	TiO ₂	(NH ₄) ₂ S ₂ O ₈	97 (86 ^d)
5	—	(NH ₄) ₂ S ₂ O ₈	0
6	TiO ₂	FeSO ₄	62
7	TiO ₂	NaHSO ₃	72
8	TiO ₂	Na ₂ SO ₃	6
9	TiO ₂	Na ₂ S ₂ O ₃	18
10	TiO ₂	(NH ₄) ₂ S ₂ O ₈ + NaHSO ₃	98

^a 0.2 mmol amine, 0.3 mmol aldehyde, 2.5 mL 1,4-dioxane, 2.5 mL H₂O, 0.25 mmol TiO₂ (P25), 6 mg additive, argon, UV, (365 nm LED), rt, 9 h.

^b Selectivity based on the peak area of GC-FID without modification. The dr ratios of the reactions were ~45:55. The conversions of all the reactions were ~100% and the major byproducts were imines.

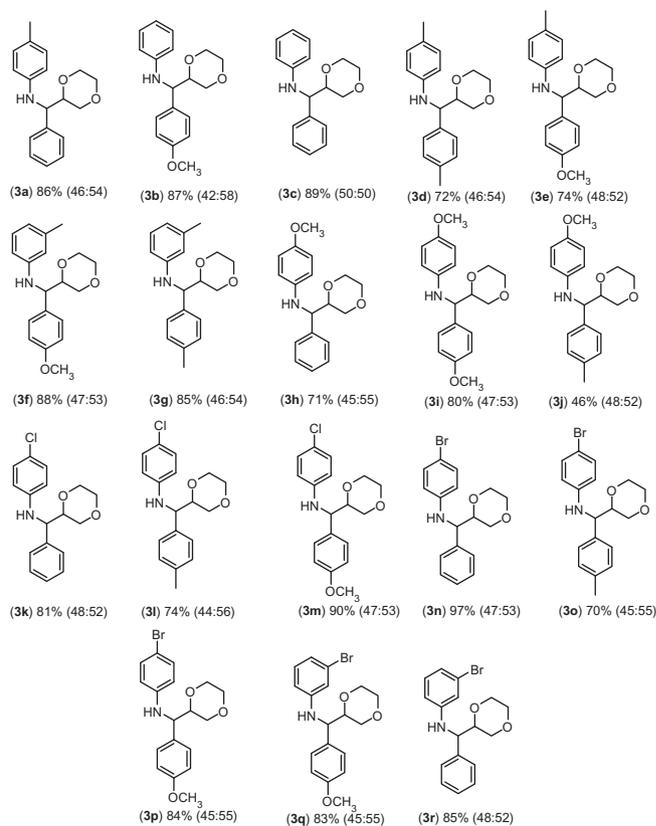
^c Without addition of H₂O.

^d Isolated yield.

of (NH₄)₂S₂O₈ as co-catalyst can promote the reaction significantly. The selectivity of **3a** was 97% and (*E*)-*N*-benzylidene-4-toluidine was observed as byproduct. Meanwhile, the isolated yield of **3a** was 86%, entries 4 and 5. Moreover, other sulfate and sulfide inorganic salts as co-catalysts were also studied but no better result was obtained, entries 6–9. It is noteworthy, as a classical combination for radical generating, the co-addition of (NH₄)₂S₂O₈ and NaHSO₃ was tested, too, and a similar result as (NH₄)₂S₂O₈ itself as co-catalyst was observed, entry 10. Thus, according to the above results, it can be concluded that the applying of TiO₂ is indispensable for the three-component reaction. Meanwhile, (NH₄)₂S₂O₈ as co-catalyst can promote the reaction.

Next, the generality of this system was explored, (Scheme 1). Initially, aniline and benzaldehyde as starting materials were tried and **3c** as the major product was obtained with 89% yields. Similar yield, that is 87%, to the desired product **3b** was obtained if the *p*-MeO group was incorporated into benzaldehyde. *p*-Toluidine also exhibited nice reactivity and 72–86% yields to **3d** and **3e** were obtained in the reactions with benzaldehyde, *p*-Me benzaldehyde or *p*-methoxybenzaldehyde and 1,4-dioxane. The use of *m*-substituted starting materials does not affect the reactivity significantly. For example, 88% and 85% isolated yields of **3f** and **3g** were obtained if *m*-toluidine was used and reacted with benzaldehyde and *p*-methoxybenzaldehyde. When *p*-methoxyaniline was employed to react with benzaldehyde and *p*-methoxybenzaldehyde, 71–80% yields to the **3h** and **3i** can be achieved. However, the yield to **3j** was only 46%. The incorporation of halide substituents into the nucleophilic addition reaction should be interesting because the presence of active C–X bonds is helpful to extend their applications in the synthesis of other compounds. Here, a series of chloro and bromo functionalized aniline derivatives as starting materials were tested. To our delight, they can react with benzaldehyde and 1,4-dioxane smoothly and **3k–3r** can be synthesized with up to 97% isolated yields. It should be mentioned that the dr ratios in all the products were close to 45:55. When *o*-toluidine was used as starting material, the selectivity to the aim product was 74% determined by GC-FID. However, we still do not get the pure products now.

This system is also very efficient in the three-component reactions of 1,3-dioxolane with different aniline and aldehyde deriva-



Scheme 1. Three-component reaction of 1,4-dioxane with aniline and benzaldehyde derivatives. 0.2 mmol amine, 0.3 mmol aldehyde, 2.5 mL 1,4-dioxane, 2.5 mL H₂O, 0.25 mmol TiO₂ (P25), 6 mg (NH₄)₂S₂O₈, UV (365 nm LED), argon, rt, 20 h. Isolated yields. Diastereomer ratios are given in parenthesis.

tives, (Table 2). Similar as the three-component reactions using 1,4-dioxane, aniline and benzaldehyde derivatives with different substituting groups can be used as the starting materials and the yields to products **4a–4j** were 65–93%, entries 1–10. The dr ratios of products using 1,3-dioxolane as nucleophile were all close to 15:85.

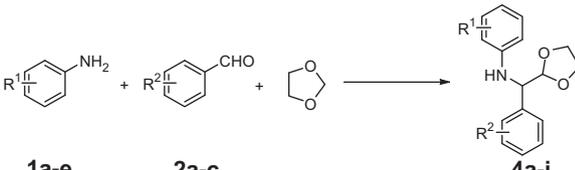
Except the syntheses of compounds **3** and **4** discussed above, THF can be used as nucleophile for the three-component reaction and the yield to **5a** was 58%. It should be mentioned that the dr ratio of **5a** was 47:53. If *o*-toluidine was used as starting material, the reaction can also be carried out and the selectivity to the aimed product was 59% determined by GC-FID.

Following, the isotope effect study was employed to explore the mechanism of the reaction, (Scheme 2). Clearly, there are four steps involved in the nucleophilic addition of THF to imine. It is the reaction of benzaldehyde and *p*-toluidine to form imine (step 1), radical generation (step 2), nucleophilic addition of radical to imine (step 3) and formation of amine product (step 4), respectively. Among the four steps, step 1 and step 4 should not be the rate determining steps because relatively a large amount of imine and amine was observed during the reaction. In addition, the ratio of (**5a** + *d*₁-**5a**):(*d*₇-**5a** + *d*₈-**5a**) was 1.30:1. This number is close to 1 and it suggests that step 2, that is the generation of THF radical, is not the rate-determining step, and we suppose that step 3 might be the rate-determining step but it cannot be confirmed at this stage. Moreover, the ratio of *d*₇-**5a** to *d*₈-**5a** is 6.15:1. That means the major deuterated product is *d*₇-**5a**, which shows remarkable proton exchange in the presence of water as solvent.

In summary, a simple and efficient method for the three-component reactions of aldehyde, amine and cyclic ethers was devel-

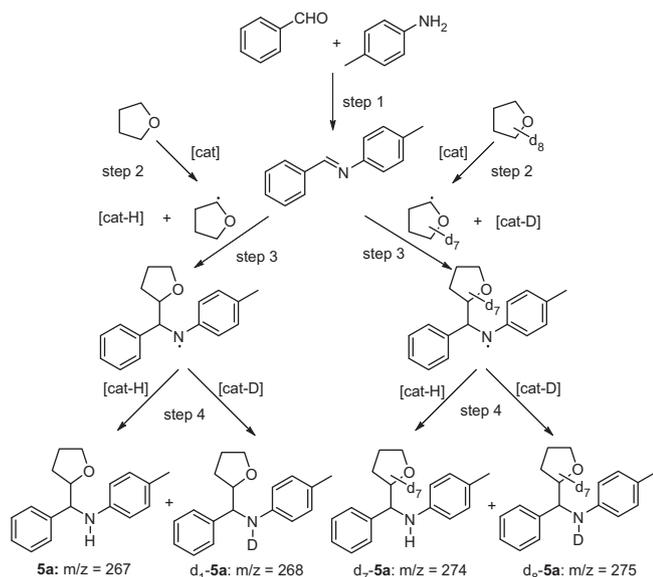
Table 2

Three-component reaction of 1,3-dioxolane with aniline and benzaldehyde derivatives^a



Entry	R ¹	R ²	Isolated yields (%) (a)
1	H (1a)	H (2a)	87%(dr = 14:86) (4a)
2	H (1a)	<i>p</i> -MeO (2b)	84%(dr = 14:86) (4b)
3	<i>m</i> -Me (1b)	H (2a)	78%(dr = 14:86) (4c)
4	<i>m</i> -Me (1b)	<i>p</i> -MeO (2b)	93%(dr = 14:86) (4d)
5	<i>p</i> -MeO (1c)	H (2a)	71%(dr = 15:85) (4e)
6	<i>p</i> -MeO (1c)	<i>p</i> -Me (2c)	78%(dr = 14:86) (4f)
7	<i>p</i> -MeO (1c)	<i>p</i> -MeO (2b)	65%(dr = 11:89) (4g)
8	<i>p</i> -Cl (1d)	<i>p</i> -MeO (2b)	75%(dr = 15:85) (4h)
9	<i>m</i> -Br (1e)	<i>p</i> -MeO (2b)	73%(dr = 19:81) (4i)
10	<i>m</i> -Br (1e)	<i>p</i> -Me (2c)	75%(dr = 19:81) (4j)

^a 0.2 mmol amine, 0.3 mmol aldehyde, 2.5 mL 1,3-dioxolane, 2.5 mL H₂O, 0.25 mmol TiO₂ (P25), 6 mg (NH₄)₂S₂O₈, UV (365 nm LED), argon, rt, 10 h. Diastereomer ratios are given in parenthesis following the yields.



$$\begin{aligned}
 \mathbf{5a} : \mathbf{d_1-5a} : \mathbf{d_7-5a} : \mathbf{d_8-5a} &= \text{Peak}_{267} : \text{Peak}_{268} : \text{Peak}_{274} : \text{Peak}_{275} \\
 &= 7.89(\pm 1.36) : 1.39(\pm 0.21) : 6.15(\pm 0.33) : 1 \\
 K_{IE} = (\mathbf{5a} + \mathbf{d_1-5a}) : (\mathbf{d_7-5a} + \mathbf{d_8-5a}) &= 1.30
 \end{aligned}$$

Scheme 2. Isotope competition reactions of THF and d₈-THF.

oped applying a simple UV promoted TiO₂–(NH₄)₂S₂O₈ system. Various benzaldehydes, anilines and cyclic ethers can be transformed into the amine products with up to 97% isolated yields. Iso-

tope effect study revealed that the rate-determining step might be the nucleophilic addition of radical to imine but not radical generation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.07.060>.

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