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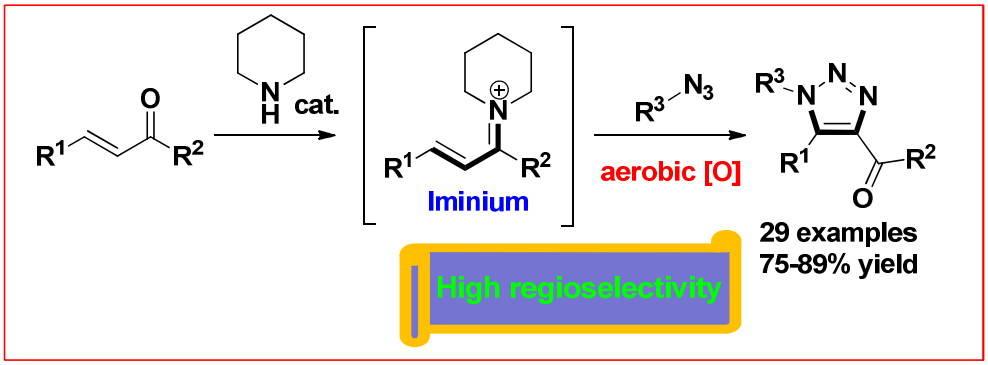
We reported a new 1,3-dipolar cycloaddition reaction of α, β-unsaturated ketones with azides through iminium catalysis in DMSO.



Organocatalytic 1,3-Dipolar Cycloaddition Reaction of α, β-Unsaturated Ketone with Azide through Iminium Catalysis

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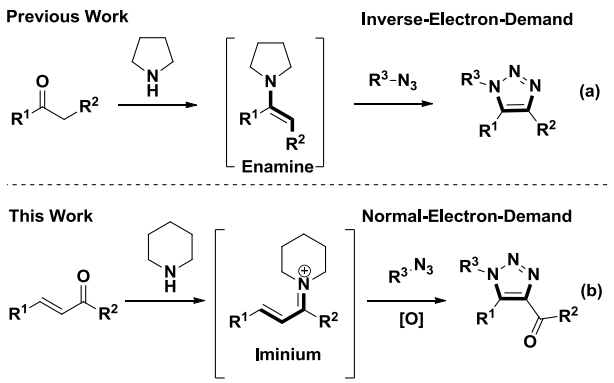
1,3-Dipolar cycloaddition reaction of α, β-unsaturated ketone with azide through iminium catalysis has been developed. This method could furnish 1,4,5-trisubstituted 1,2,3-triazoles in good yields and high levels of regioselectivities.

Heterocycles have attracted much attention from scientists because of their various biological activities.[1] As one of the most important heteroaromatic compounds, 1,2,3-triazoles have exhibited considerably biological and pharmaceutical activities.[2] As showed in Fig 1, Tazobactam is a pharmaceutical drug that inhibits the action of bacterial β-lactamases.[3] Cefatrizine exhibits antibacterial activity.[4] Besides, 1,2,3-Triazole moieties are also disclosed as NMDA receptor antagonist and IAG-NH inhibitor.[5] Therefore, developing efficient and practical method to construct 1,2,3-triazole moieties is a significant and challenging work.

The widely used protocol to synthesize 1,2,3-triazole is the Huisgen 1,3-dipolar cycloaddition.[6] Although this method has an advantage of simple operation, it provides a mixture of two regioisomers. In 2002, Meldal[7] and Sharpless[8] groups independently developed a Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) method to construct 1,2,3-triazole in an excellent level of regioselectivity. However, the copper ions are potentially toxic for living organisms[9] and could induce degradation of viruses.[10] Therefore, developing novel method to overcome these drawbacks is the significant responsibility of chemists. In recent years, Ramachary[11], Bressy[12] and our group[13] independently reported the enamine-catalyzed organocatalytic 1,3-dipolar cycloaddition of ketones to azides to generate highly substituted 1,2,3-triazoles (Scheme 1a).[14] This strategy could not only provide the 1,2,3-triazoles in high yields and regioselectivities,



Scheme 1. Organocatalytic strategies in preparation of 1,2,3-triazoles.

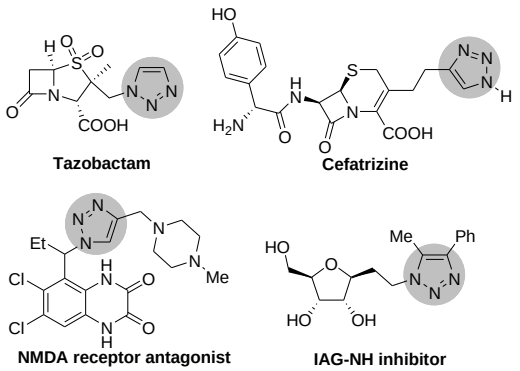


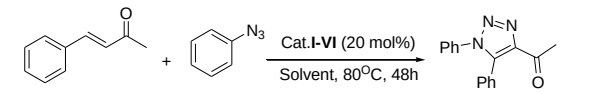
Fig 1: Examples of important 1,2,3-triazoles.

but also avoid to utilize toxic metal catalysts. However, we realize that these previous works are very restricted to ketones or cyclic enone substrates, which have largely limited their applications.[11,12,13a-b] As our continued interests in this area, especially in expanding substrate scope and reaction type,[13c-e] herein, we report our recent progress regarding to iminium-catalyzed cycloadditions of azides to α, β-unsaturated ketones, which are promoted by an active iminium intermediate (Scheme 1b).[15, 16]

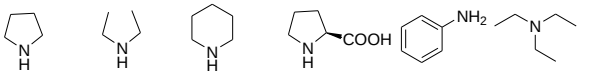
We began our initial investigation by employing α, β-unsaturated ketone **1a** and phenyl azide **2a** in the presence of various amine catalysts, including secondary amines (**I**-**IV**), primary amine (**V**) and tertiary amine (**VI**). The screening results indicated that secondary amine **III** was the best catalyst for this reaction (Table 1, entry 3). The primary amine (**V**), tertiary amine (**VI**) and other secondary amines (**I** and **IV**) gave ~~the~~ poor results (Table 1, entries 1, 4-6). Next we utilized secondary amine **III** as the best catalyst to screen ~~the~~ solvent. Further experimental results revealed that ~~the~~ solvent was one of the crucial factors for this reaction. For example, ~~when the reaction was conducted in~~ DMSO~~, the solvent~~ gave the positive influence on this reaction and afforded the desired product **3aa** in 55% yield (Table 1, entry 3). Changing the solvents to toluene and $CHCl_3$, the yields ~~would~~ decreased to 48% and 34% respectively (Table 1, entries 8-9). However, almost no reaction happened if methanol, THF, dioxane and H_2O were used as reaction medium (Table 1, entries 10-13). In order to improve the chemical yield, we then changed the ratio of **1a**:**2a**. The experimental results shown that the ratio of **1a**:**2a** was found to be another crucial factor. When we changed the ratio of **1a**:**2a** from 1:1.2 to 1:1.5, the yield ~~would~~

increased from 55% to 68% ~~in the same reaction time~~ (Table 1, entry 14). To our delight, if we increased the amount of **2a** to 2.0 equivalents, the yield increased to 84% (Table 1, entry 15). Then we conducted the reaction at 100 °C for 48 h using 2.0 equivalents of **2a**. However, the yield slightly decreased to 78% (Table 1, entry 16), which may be caused by the plausible decomposition of **2a**. Lowering the catalyst loading to 10 mol%, a similar result (82% yield) was observed in a prolonged reaction time (Table 1, entry 17). Further reducing the catalyst loading to 5 mol%, a 75% yield was still achieved after 72 h (Table 1, entry 18). Finally, the best result was obtained in the presence of 10 mol% of cat. **III** and **1a**:**2a** = 1.0:2.0 at 80 °C using DMSO as solvent (Table 1, entry 17).

Table 1: Optimization of the reaction conditions.[a]



1a **2a** **3aa**



I **II** **III** **IV** **V** **VI**

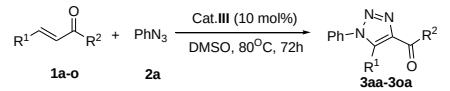
Entry	Cat.	Solvent	t/h	Yield[b](%)
1	**I**	DMSO	48	11
2	**II**	DMSO	48	43
3	**III**	DMSO	48	55
4	**IV**	DMSO	48	21
5	**V**	DMSO	48	38
6	**VI**	DMSO	48	22
7	**III**	DMF	48	52
8	**III**	Toluene	48	48
9	**III**	$CHCl_3$	48	34
10	**III**	MeOH	48	<5
11	**III**	THF	48	<5
12	**III**	Dixoane	48	<5
13	**III**	H_2O	48	<5
14[c]	**III**	DMSO	48	68
15[d]	**III**	DMSO	48	84
16[e]	**III**	DMSO	48	78
17[d,f]	**III**	DMSO	72	82
18[d,g]	**III**	DMSO	72	75

[a] Reaction conditions: A mixture of **1a** (0.10 mmol), **2a** (0.12 mmol) and catalyst (20 mol%) in the solvent (0.3 mL) was stirred at 80 °C for 48h. [b] Isolated yield. [c] **1a**:**2a** = 1.0:1.5. [d] **1a**:**2a** = 1.0:2.0. [e] **1a**:**2a** = 1.0:2.0 at 100 °C. [f] 10 mol% catalyst used. [g] 5 mol% catalyst used.

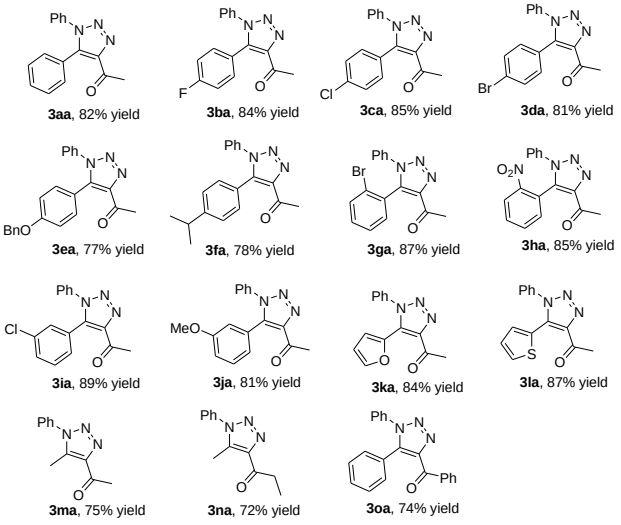
With the optimized reaction conditions in hand, we then investigated the scope of α, β-unsaturated ketones **1** and azide **2a**. As summarized in table 2, the reaction is general for aromatic α, β-unsaturated ketones **1a-j**, no matter what the substitution patterns are electron-donating or electron-withdrawing properties, the corresponding products were obtained in good to high yields (Table 2, **3aa-3ja**, 77-89%). It is noteworthy that heterocyclic rings such as furan and thiophene rings were also tolerated in substrates, affording the desired products in high yields (Table 2, **3ka-3la**, 84-87%). Notably, for less reactive α, β-unsaturated alkyl ketones **1m** and **1n**, good yields were also obtained (Table 2, **3ma-3na**, 75-72%). Pleasingly, chalcone **1o** was also found to be a suitable partner to afford the corresponding product **3oa** in 74% yield.

Encouraged by above results, the generality of azides was then evaluated. As shown in table 3, the aromatic azides, including electron-donating groups and electron-withdrawing groups were

Table 2: Scope of α, β-unsaturated ketones.[a]



1a-o **2a** **3aa-3oa**



3aa, 82% yield **3ba**, 84% yield **3ca**, 85% yield **3da**, 81% yield

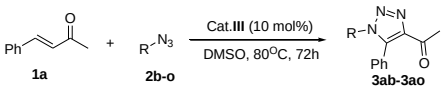
3ea, 77% yield **3fa**, 78% yield **3ga**, 87% yield **3ha**, 85% yield

3ia, 89% yield **3ja**, 81% yield **3ka**, 84% yield **3la**, 87% yield

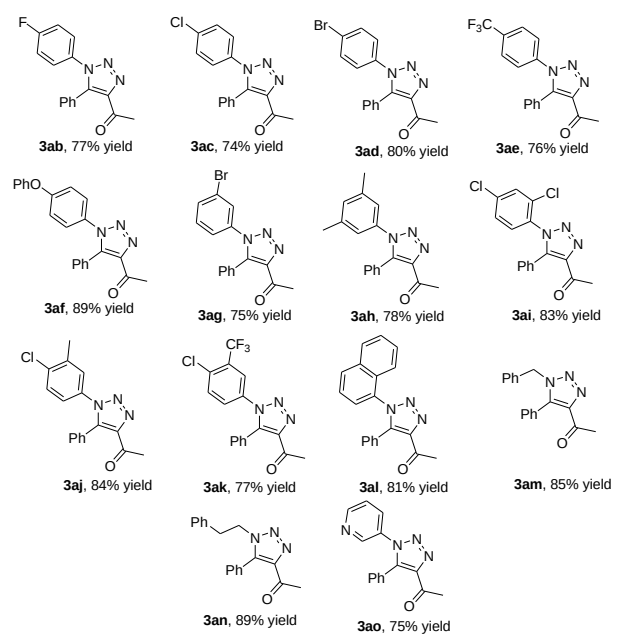
3ma, 75% yield **3na**, 72% yield **3oa**, 74% yield

[a] Reaction conditions: A mixture of **1a-o** (0.10 mmol), **2a** (0.20 mmol) and **III** (10 mol%) in DMSO (0.3 mL) was stirred at 80 °C for 72h.

Table 3: Scope of azides.[a]



1a **2b-o** **3ab-3ao**



3ab, 77% yield **3ac**, 74% yield **3ad**, 80% yield **3ae**, 76% yield

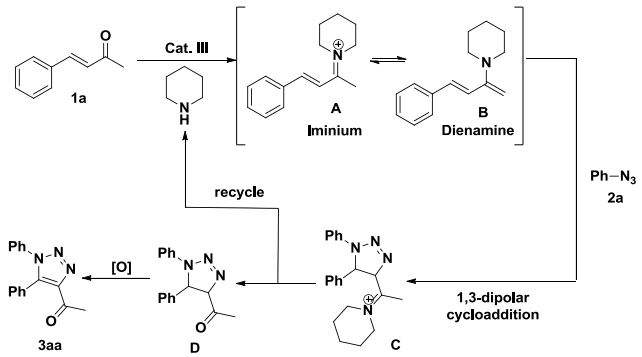
3af, 89% yield **3ag**, 75% yield **3ah**, 78% yield **3ai**, 83% yield

3aj, 84% yield **3ak**, 77% yield **3al**, 81% yield **3am**, 85% yield

3an, 89% yield **3ao**, 75% yield

[a] Reaction conditions: A mixture of **1a** (0.10 mmol), **2b-o** (0.2 mmol) and **III** (10 mol%) in DMSO (0.3 mL) was stirred at 80 °C for 72h.

all tolerated for this reaction, giving the desired products in high yields (Table 3, **3ab-3ak**, 74-89%). To our delight, naphthalene ring and heterocyclic ring also exhibited high reactivities to afford the corresponding product **3al** and **3ao** in 81% and 75% yields respectively. In addition, when alkyl azides **2m** and **2n** were used as the substrates, the reactions also proceeded smoothly to give the desired products in high yields (Table 3, **3am-3an**, 85-89%). The configuration was assigned unambiguously by X-ray analysis on the triazole derivative of **3da** (See Table 2).[17]



Scheme 2. Plausible mechanism.

As showed in scheme 2, a plausible mechanism is proposed to explain the reaction process. First of all, α, β-unsaturated ketone **1a** reacts with catalyst **III** to form the iminium intermediate **A**, which could be transferred to dienamine intermediate **B**. Then 1,3-dipolar cycloaddition reaction takes place between iminium intermediate **A** and azide **2a** to form the intermediate **C**, which release the catalyst **III** to generate the intermediate **D**. Susequently, an aerobic oxidation of intermediate **D** generates the final product **3aa**.

In summary, an iminium-catalyzed 1,3-dipolar cycloaddition of azide to α, β-unsaturated ketone has been developed. The reaction is catalyzed by a simple and cheap catalyst to give substituted 1,2,3-triazoles in high yields and excellent levels of regioselectivities. Considering the ready availability of the starting materials (α, β-unsaturated ketones) and the operational simplicity, we believe that this method will have a broad use. Further mechanistic and applications of this reaction are ongoing in our group, and more results will be reported in due course.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (*a*) J. W. Black, G. I. Durant, J. C. Emmett and C. R. Ganellin, *Nature*, 1974, **248**, 65; (*b*) S. A. Laufer, W. Zimmermann and J. Ruff, *J. Med. Chem.*, 2004, **47**, 6311.
2 For selected reports and reviews, see: (*a*) R. Kharb, P. C. Sharma and M. S. Yar, *J. Enzyme Inhib. Med. Chem.*, 2011, **26**, 1; (*b*) R. S. Bohacek, C. McMartin and W. C. Guida, *Med. Res. Rev.*, 1996, **16**, 3; (*c*) M. Meldal and C. W. Tornoe, *Chem. Rev.*, 2008, **108**, 2952; (*d*) Y. L. Angell and K. Burgess, *Chem. Soc. Rev.*, 2007, **36**, 1674; (*e*) F. Pagliai, T. Pirali, E. D. Grosso, R. D. Brisco, G. C. Tron, G. Sorba and A. A. Genazzani, *J. Med. Chem.*, 2006, **49**, 467; (*f*) T. Lee, M. Cho, S.-Y. Ko, H.-J. Youn, D. J. Baek, W.-J. Cho, C.-Y. Kang and S. Kim, *J. Med. Chem.*, 2007, **50**, 585; (*g*) G. Smith, M. Glaser, M. Perumal, Q.-D. Nguyen, B. Shan, E. Arstad and E. O. Aboagye, *J. Med. Chem.*, 2008, **51**, 8057; (*h*) C.-B. Yim, I. Dijkgraaf, R. Merkx, C. Versluis, A. Eek, G. E. Mulder, D. T. S. Rijkers, O. C. Boerman and R. M. J. Liskamp, *J. Med. Chem.*, 2010, **53**, 3944.
3 F. J. Legat, R. Krause, P. Zenahlik, C. Hoffmann, S. Scholz, W. Salmhofer, J. Tscherpel, T. Tscherpel, H. Kerl and P. Dittrich, *Antimicrob. Agents Chemother.*, 2005, **49**, 4368.
4 (*a*) H. C. Neu and K. P. Fu, *Antimicrob. Agents Chemother.*, 1979, **15**, 209; (*b*) C. C. Blackwell, E. H. Freimer and G. C. Tuke, *Antimicrob. Agents Chemother.*, 1976, **10**, 288.
5 (*a*) M. J. Fray, D. J. Bull, C. L. Carr, E. C. L. Gautier, C. E. Mowbray and A. Stobie, *J. Med. Chem.*, 2001, **44**, 1951; (*b*) D. K. Mohapatra, P. K. Maity, M. Shabab and M. I. Khan, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5241; (*c*) C. Gill, G. Jadhav, M. Shaikh, R. Kale, A. Ghawalkar, D. Nagargoje and M. Shiradkar, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6244.
6 (*a*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565; (*b*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 633.
7 C. W. Tornoe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.
8 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596.
9 K. Jomova and M. Valko, *Toxicology*, 2011, **283**, 65.
10 (*a*) Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless and M. G. Finn, *J. Am. Chem. Soc.*, 2003, **125**, 3192; (*b*) J. Gierlich, G. A. Burley, P. M. E. Gramlich, D. M. Hammond and T. Carell, *Org. Lett.*, 2006, **8**, 3639.
11 (*a*) D. B. Ramachary, K. Ramakumar and V. V. Narayana, *Chem.-Eur. J.*, 2008, **14**, 9143; (*b*) D. B. Ramachary and A. B. Shashank, *Chem.-Eur. J.*, 2013, **19**, 13175; (*c*) D. B. Ramachary, A. B. Shashank and S. Karthik, *Angew. Chem. Int. Ed.*, 2014, **53**, 10420.
12 M. Belkheira, D. El Abed, J.-M. Pons and C. Bressy, *Chem.-Eur. J.*, 2011, **17**, 12917.
13 (*a*) L. J. T. Danence, Y. Gao, M. Li, Y. Huang and J. Wang, *Chem.-Eur. J.*, 2011, **17**, 3584; (*b*) L. Wang, S. Y. Peng, L. J. T. Danence, Y. Gao and J. Wang, *Chem.-Eur. J.*, 2012, **18**, 6088; (*c*) W. J. Li, Q. F. Jia, Z. Y. Du and J. Wang, *Chem. Commun.*, 2013, **49**, 10187; (*d*) D. K. J. Yeung, T. Gao, J. Y. Huang, S. F. Sun, H. B. Guo and J. Wang, *Green Chem.*, 2013, **15**, 2384; (*e*) L. Wang, J. Y. Huang, X. J. Gong and J. Wang, *Chem.-Eur. J.*, 2013, **19**, 7555; (*f*) W. J. Li, Z. Y. Du, J. Y. Huang, Q. F. Jia, K. Zhang and J. Wang, *Green Chem.*, 2014, **16**, 3003; (*g*) W. J. Li and J. Wang, *Angew. Chem. Int. Ed.* 2014, DOI: 10.1002/anie.201408265R1.
14 For other related examples, see: (*a*) N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão and D. Alves, *Eur. J. Org. Chem.* 2014, 1059; (*b*) N. Seus, L. C. Goncalves, A. M. Deobald, L. Savegnago, D. Alves and M. W. Paixao, *Tetrahedron* 2012, **68**, 10456; (*c*) J. John, N. Parekh and W. Dehaen, *Angew. Chem. Int. Ed.*, 2014, **53**, 10155; (d) A. Ali; A. G. Corrêa; S. Alves; J. Zukerman-Schpector; B. Westermann, M. A. B. Ferreira and M. W. Paixão. *Chem. Commun*. 2014, **50**, 11926.
15 For selected examples of activated olefins or preformed enolates with aryl/alkyl azides, see: (*a*) C. D. Bedford, E. M. Bruckmann and P. A. S. Smith, *J. Org. Chem.* 1981, **46**, 679; (*b*) F. Stazi, D. Cancogni, L. Turco, P. Westerduin and S. Bacchi, *Tetrahedron Lett.* 2010, **51**, 5385; (*c*) Y. A. Rozin, J. Leban, W. Dehaen, V. G. Nenajdenko, V. M. Muzalevskiy, O. S. Eltsov and V. A. Bakulev, *Tetrahedron* 2012, **68**, 614; (*d*) H. Singh, J. Sindhu and J. M. Khurana, *RSC Adv*. 2013, **3**, 22360; (*e*) A. Kayet and T. Pathak, *J. Org. Chem.* 2013, **78**, 9865; (*f*) S. Dey and T. Pathak, *RSC Adv*. 2014, **4**, 9275.
16 For selected examples of organocatalytic reactions using iminium catalysis, see: (*a*) K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc*., 2000, **122**, 4243; (*b*) W. S. Jen, J. J.

M. Wiener and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 9874; (*c*) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964.

17 CCDC 1021699 (**3da**) contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, Fax: +44(1223)336033.