TBD-organocatalysed synthesis of pyrazolines†

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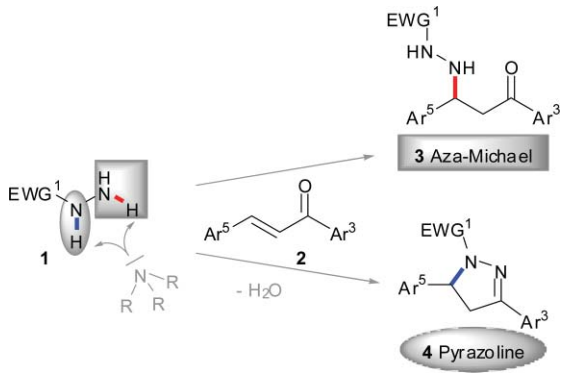
It was found that TBD, a cheap and commercially available guanidine, easily catalysed the synthesis of biologically important 3,5-diarylpyrazolines from chalcones and acylhydrazines *via* a selective secondary amine alkylation.

The 3,5-diarylpyrazoline scaffold **4** (Scheme 1) is displayed within an increasing number of bioactive compounds acting as inhibitors of the mitotic kinesin KSP,[1a] mycobacterium tuberculosis[1b] and West Nile viruses,[1c] and those with insecticidal activities,[1d] *etc.*[2–3] The Δ^2-pyrazoline ring is usually synthesised *via* [2+3] cycloadditions of diazoalkane or nitrilimine dipoles,[2–3] although alternative methodologies are emerging.[4] On the other hand, the construction of 3,5-diarylpyrazolines chiefly relies on the cyclocondensation of hydrazines, having electron-rich aryl or alkyl groups, with chalcones **2** under acidic conditions.[3,5] Nevertheless, in medicinal chemistry, the presence of an electron-withdrawing polar functional group on N^1 (**4**) markedly impacts on both the selectivities and affinities of pyrazoline ligands through hydrogen bonding or electrostatic interactions.[1] The method of choice for their synthesis consists of using an excess of hydrazine hydrate, giving 1*H*-pyrazolines, followed by the condensation of acyl chloride, isocyanate and sulfonyl chloride derivatives.[1,3,6] The isolation of the rather instable 1*H*-pyrazolines[6] was avoided by performing the reaction in a refluxing acetic acid solution, giving rise to the formation of the more robust acetyl diazoles **4** (EWG^1 = Ac) and,[1,5b] in some cases, to higher acetyl homologues (EWG^1 = EtCO, Bz).[5b,7] The (thio)-semicarbazides were also successfully added to chalcones in the presence of strong sodium hydroxide base or HCl.[8] In this context, the development of alternative and less drastic reaction conditions would be helpful for the elaboration of a larger array of 3,5-diarylpyrazolines **4**.

With regard to the usefulness of mono-substituted hydrazines in organic synthesis,[9] the regioselective catalytic functionalisation of only one nitrogen atom constitutes an attractive synthetic challenge toward heterocylic compound elaboration. Aiming at exploiting the base-catalysed aza-Michael process (Scheme 1),[10] we sought an amine suitably enabled to selectively 'activate' the N^1–H bond of hydrazine nucleophiles **1** toward chalcones. Accordingly, a cyclocondensation into pyrazolines **4** would take place instead of the expected conjugate addition of the primary amine moiety to form product **3**.[11] Therefore, we would have in our hands a straightforward and organocatalytic[12] synthesis of 3,5-diarylpyrazolines, simply releasing water and without the possibility of any metal contamination, making products suitable for further pharmaceutical evaluation.[10b–c] In fact, elegant precedents described the N^1 selective alkylation of mono-substituted hydrazines but made use of an excess of inorganic bases,[13] and employed transition metals.[14] Also worthy of note is the asymmetric conjugate addition of electron-rich hydrazines promoted by Lewis acids, developed respectively by Sibi and Kanemasa,[15] who thereby achieved pyrazolidinone and pyridyl-substituted pyrazoline syntheses.



Scheme 1 Regioselective alkylation of hydrazines.

In order to validate our working hypothesis, we evaluated the ability of several amines (with increased pK_a values) to catalyse the reaction between acetylhydrazine **1a** and chalcone **2a** at 60 °C in toluene (Table 1). At the onset, it was shown that the aza-Michael product **3a** was formed *via* a background reaction (entry 1), but, DABCO, quinuclidine and DMAP (entries 2–4) increased, to some extent, the formation rate of **3a** without giving any acetylpyrazoline **4a**. By means of the more basic DBU base (entry 5), traces of **4a** were formed. Therefore, we turned our attention to stronger guanidine bases.[16] Although TMG and MTBD (entries 6–7) mainly furnished **3a**, pleasingly, TBD (entry 8) achieved an 86% yield of pyrazoline **4a**. Increasing the catalyst loading from 10 to 20% secured a complete transformation into **4a** in 93% yield (entry 9). Importantly, this reaction is smoothly performed without using any large excess of reactants and all partners are cheap and commercially available. The catalytic activity of TBD *vs* MTBD or TMG is remarkable and may be ascribed to both its high pK_a and its Brønsted acid–base properties (*vide infra*).[17]

Further optimisation revealed that the reaction was slightly faster in acetonitrile but decreasing the temperature to 40 °C slowed down the process (see ESI†). Therefore, we evaluated various EWG-substituted hydrazines **1a–1h** with 10% of TBD in acetonitrile at 60 °C (Table 2)‡. Thus, the formation of pyrazolines

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Table 1 Addition of acetylhydrazine **1a** to chalcone **2a** (EWG[1] = Ac; Ar = Ph)[a]

Entry	Amine base (0.1 equiv.)	Aza-Michael **3a** (%)[b]	Pyrazoline **4a** (%)[b]
1	—	41	0
2	DABCO	72	0
3	DMAP	69	0
4	Quinuclidine	68	0
5	DBU	68	5
6	TMG[c]	75	3
7	MTBD[d]	54	11
8	TBD[e]	9	86
9	TBD[f]	0	93

[a] All reactions were performed with 0.25 mmol of chalcone **2a** (0.5 M) with acetylhydrazine **1a** (1.1 equiv.), amine base (0.1 equiv.) in anhydrous toluene at 60 °C for 17 h. [b] NMR yield with an internal standard. [c] *N*,*N*,*N*′,*N*′-tetramethylguanidine. [d] 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene. [e] 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [f] 0.2 equiv. of TBD for 23 h.

Table 2 Addition of hydrazines **1** to chalcone **2a** (Ar = Ph)[a]

Entry	EWG[1] (1.2 equiv.)	Pyrazolines **4** (%)[b]
1	COMe (**1a**)	82 (**4a**)
2	COPh (**1b**)	80 (**4b**)
3	COO*t*-Bu (**1c**)	88 (**4c**)
4	CO-2-furyl (**1d**)	79 (**4d**)
5	CO-4-Pyr (**1e**)	66 (**4e**)[c,d]
6	CONHPh (**1f**)	97 (**4f**)
7	$CSNH_2$ (**1g**)	81 (**4g**)
8	Ts (**1h**)	20 (**4h**)[e]

[a] 1 mmol of chalcone **2a** (1 M) with hydrazine derivative **1** (1.2 equiv.), TBD (0.1 equiv.) in anhydrous acetonitrile at 60 °C for 24 h. [b] Isolated yield after column chromatography. [c] 0.2 equiv. of TBD was used. [d] Conversion of 75% after 24 h with 0.1 equiv. of TBD. [e] NMR yield with an internal standard.

having acetyl (entry 1), benzoyl (entry 2), acid sensitive Boc (entry 3) and carboxy-2-furyl (entry 4) functional groups on the nitrogen was achieved with 79 to 88% yields. The reaction of 4-pyridinecarboxylic acid hydrazide turned out to be more sluggish and required 20% of TBD to reach a complete transformation in 24 hours (entry 5). Semicarbazide and thiosemicarbazide (entries 6–7) smoothly added to chalcone with 97 and 81% yields respectively. Despite the large scope of the methodology, tosylhydrazine (entry 8) gave **4h** in low yield along with an inseparable mixture of products. It is assumed that an elimination of sulfinate took place, affording diimide (gas evolution was observed) followed by some reduction events.[18]

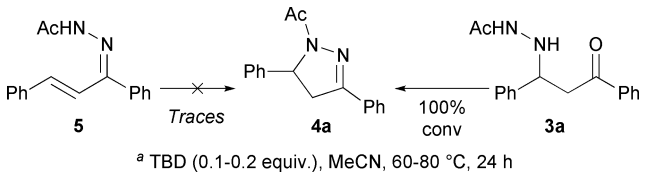
Subsequently, we performed the addition of acetylhydrazine **1a** to various chalcone derivatives **2** (Table 3). These conditions were tolerant to *para*- (entries 1, 3 and 5–6), *ortho*-substituted aryl (entries 2 and 9) and heteroaromatic groups (entries 4 and 7) at pyrazoline C^3 and C^5. On the other hand, the reaction was less fruitful with electron-poor aryl groups at C^5 and the limit was observed with a *para*-nitroaryl moiety (entry 8). In this case, the reaction was not clean and the pyrazoline **4p** turned out to be unstable on silica gel.

In order to get an insight into the mechanism of this transformation, we performed two test reactions (Scheme 2). In the presence of TBD, the known unsaturated hydrazone[11] **5** led to traces of pyrazoline **4a**, ruling out the condensation of hydrazine **1a** to chalcone **2a** before cyclisation.[19] However, the aza-Michael derivative **3a** was quantitatively transformed into **4a**. In fact, a cross-over experiment conducted in the presence of 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one **2k** led to 33% of fluoropyrazoline **4k** besides pyrazoline **4a**, which suggested an equilibrated process between **3a** and starting materials **1a** and **2a** (see ESI† for further details).

Table 3 Addition of acetylhydrazine **1a** to various chalcones **2**[a]

Entry	Chalcones **2**	Ar^3	Ar^5	Pyrazolines **4**[b]
1	**2i**	4-$MeOC_6H_4$	Ph	81% (**4i**)
2	**2j**	2-$MeOC_6H_4$	Ph	78% (**4j**)
3	**2k**	4-FC_6H_4	Ph	84% (**4k**)
4	**2l**	2-Thienyl	Ph	69% (**4l**)
5	**2m**	Ph	4-ClC_6H_4	68% (**4m**)
6	**2n**	Ph	4-$MeOC_6H_4$	81% (**4n**)
7	**2o**	Ph	2-Thienyl	77% (**4o**)
8	**2p**	Ph	4-$NO_2C_6H_4$	<20% (**4p**)[c,d]
9	**2q**	Ph	2-MeC_6H_4	83% (**4q**)

[a] 1 mmol of chalcone **2** (1 M) with acetylhydrazine **1a** (1.2 equiv.), TBD (0.1 equiv.) in anhydrous acetonitrile at 60 °C for 24 h. [b] Isolated yield after column chromatography. [c] 48 h with 0.2 equiv of TBD. [d] 10% of aza-Michael product **3p** was isolated.



Scheme 2 Mechanistic investigations.

This led us to perform an *in situ* infrared spectroscopy study (ReactIR technology) in order to follow up the formation of both **3a** and **4a** *versus* time in the presence of 20% of TBD in acetonitrile at 60 °C (full details in the ESI†). As depicted in Fig. 1, the rapid disappearance of chalcone **2a** was easily monitored with the ν(C=C) vibrations at 1609 cm^{-1}. Although the absorption at 1683 cm^{-1} corresponds to the overlapping of both acetylhydrazine **1a** and aza-Michael **3a** vibrations, the increase

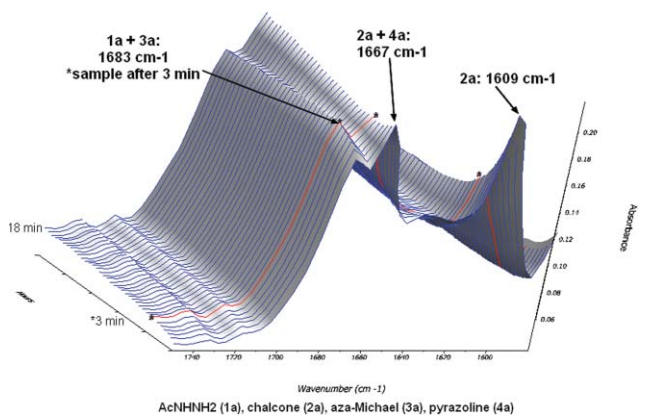
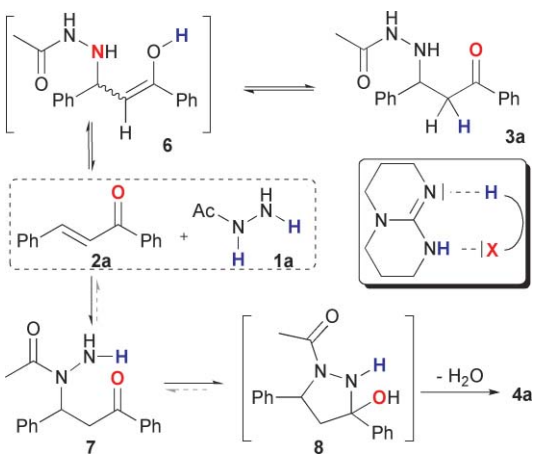


Fig. 1 (Only spectra from *1750 to 1580 cm^{-1}* over the first *18 minutes* are shown for clarity). 1683 cm^{-1}: a*za-Michael* **3a** and *acetylhydrazine* **1a**. (*) A sample analyzed by NMR after 3 min giving **2a**/**3a**/**4a** = 51/40/9. 1667 cm^{-1}: *chalcone* **2a** and *pyrazoline* **4a**. 1609 cm^{-1}: *chalcone* **2a**.

in intensity during the first minutes might account for the rapid transformation of **1a** to **3a**, which parallels the chalcone peak shrinking at 1609 cm^{-1}. Indeed, a sample was analysed by ^1H NMR after 3 minutes (roughly the intensity maximum) revealing the presence of **2a**/**3a**/**4a** in a ratio of 51/40/9 respectively (see the ESI† for further experiments). One can notice that both ν(C=O) of **4a** and **2a** are concomitantly detected at 1667 cm^{-1}. This vibration profile *versus* time shows a decrease in intensity at the beginning, corresponding to the consumption of **2a**, followed by an increasing intensity owing to the formation of **4a**. The complementary shapes of the vibration waves at 1683 cm^{-1} (**1a**+**3a**) and 1667 cm^{-1} (**2a**+**4a**) suggest that pyrazoline **4a** originates from a pre-equilibrated mixture of **3a**, **2a** and **1a** derivatives.

Accordingly, we propose the following mechanism (Scheme 3). The aza-Michael adduct **3a** is rapidly formed as the kinetic product in equilibrium with the starting materials **1a** and **2a** *via* **6**.[20] Meanwhile, upon the selective N^1–H bond activation by TBD, the conjugate addition of the secondary amine moiety of **1a** occurs, giving rise to the formation of **7** which subsequently cyclises into pyrazoline **4a**. The superior efficiency of the guanidine TBD at promoting the overall process may be attributed to its higher pK_a in comparison with the other bases.[21] However, it is difficult to find clear-cut information as to whether TBD catalyses the reaction by deprotonating the N^1–H of hydrazine **1a** or simply by assisting the aza-Michael step through transient N–H bond coordination.[22] Furthermore, the difference between the TBD and MTBD reactivity underlines a likely bifunctional catalysis.[17] One might envisage that TBD acts as a proton shuttle by facilitating the transport of a hydrogen atom (Scheme 3) in the carbon–nitrogen bond formation (**2a** to **7** and **8**) up to the dehydrating event. This last irreversible step secures the end of the process. On the other hand, the action of TBD in the retro-aza-Michael step (**3a** to **6** and **2a**) cannot be ruled out. Moreover, the α-effect of hydrazine might also help to promote the aza-Michael reaction.[23] Further investigations are required to probe all the mechanistic aspects but the use of chiral guanidines could be envisaged for developing an original asymmetric organocatalysed synthesis of pyrazoline derivatives.



Scheme 3 Mechanistic proposal.

In summary, it was found that TBD base efficiently catalyses the cyclocondensation of *N*-acylhydrazine derivatives **1** with chalcones to yield various 3,5-diarylpyrazolines **4** possessing an electron-withdrawing functional group on the N^1 nitrogen. This study highlights the ability of the TBD guanidine to promote the regioselective alkylation of the secondary amine moiety of hydrazines **1**, while the other amine bases tested promote an aza-Michael reaction (*via* the primary amine addition). This straightforward metal-free methodology would be useful for the rapid synthesis of pyrazolines in medicinal chemistry.

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Notes and references

‡ Representative procedure for the synthesis of 1-acetyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole **4a**. Chalcone (214.5 mg, 1.0 mmol, 1 equiv.), acetylhydrazine (98.8 mg, 1.2 mmol, 1.2 equiv.) and triazabicyclo[4.4.0]dec-5-ene (TBD, 13.9 mg, 0.1 mmol, 0.1 equiv.) were introduced into a Schlenk tube under nitrogen. Then, 1 mL of anhydrous acetonitrile was added at room temperature and the solution was heated at 60 °C (oil bath temperature) for 24 h. The reaction mixture was allowed to stand at room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/petroleum ether 2:3, $R_f = 0.33$) to afford the desired pyrazoline **4a** as a white powder (216.4 mg, 82%). m.p. 124–126 °C (lit.,[24] 125–125.5 °C). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.14–3.22 (dd, $J = 4.5$ Hz and 17.7 Hz, 1H), 3.72–3.82 (dd, $J = 11.8$ Hz and 17.7 Hz, 1H), 5.58–5.63 (dd, $J = 4.5$ Hz and 11.8 Hz, 1H), 7.23–7.36 (m, 5H), 7.42–7.46 (m, 3H), 7.74–7.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 22.1 (CH3), 42.4 (CH), 60.0 (CH2), 125.6 (CH), 126.6 (CH), 127.67 (CH), 128.8 (CH), 128.9 (CH), 130.4 (CH), 131.5 (C), 141.9 (C), 153.9 (C), 168.9 (C). IR (KBr) ν (cm^{-1}) 1656, 1645, 1596, 1455, 1443, 1410, 1360, 1327, 762, 691. HRMS *m*/*z* calcd for $C_{17}H_{17}N_2O_1$ $[M+H]^+$: 265.1341, found: 265.1349. *Remark*: the obtained solids tend to retain solvents such as AcOEt or CH_2Cl_2, so they have to be dried for long period of time under vacuum.

1 (*a*) C. D. Cox, M. Torrent, M. J. Breslin, B. J. Mariano, D. B. Whitman, P. J. Coleman, C. A. Buser, E. S. Walsh, K. Hamilton, M. D. Schaber, R. B. Lobell, W. Tao, V. J. South, N. E. Kohl, Y. Yan, L. C. Kuo, T. Prueksaritanont, D. E. Slaughter, C. Li, E. Mahan, B. Lu and G. D. Hartman, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3175; (*b*) M. Ashraf and M. Shaharyar, *Bioorg. Med. Chem.*, 2007, **15**, 1896; (*c*) J. R. Goodell, F. Puig-Basagoiti, B. M. Forshey, P.-Y. Shi and D. M. Ferguson, *J. Med. Chem.*, 2006, **49**, 2127; (*d*) P.-L. Zhao, F. Wang, M.-Z. Zhang, Z.-M. Liu, W. Huang and G.-F. Yang, *J. Agric. Food Chem.*, 2008, **56**, 10767.

2 Selected recent examples of cycloadditions: (*a*) S. Manyem, M. P. Sibi, G. H. Lushington, B. Neuenswander, F. Schoenen and J. Aubé, *J. Comb. Chem.*, 2007, **9**, 20; (*b*) Y. Wang, C. I. Rivera Vera and Q. Lin, *Org. Lett.*, 2007, **9**, 4155 and references cited therein. Reviews on cycloadditions:; (*c*) H. Pellissier, *Tetrahedron*, 2007, **63**, 3235; (*d*) M. Bonin, A. Chauveau and L. Micouin, *Synlett*, 2006, 2349.

3 A recent review on pyrazolines: A. Lévai, *J. Heterocyclic Chem.*, 2002, **39**, 1.

4 For selected examples: (*a*) K. Alex, A. Tillack, N. Schwarz and M. Beller, *Org. Lett.*, 2008, **10**, 2377; (*b*) S.-L. Cui, J. Wang and Y.-G. Wang, *Org. Lett.*, 2008, **10**, 13; (*c*) J. M. de los Santos, Y. López, D. Aparicio and F. Palacios, *J. Org. Chem.*, 2008, **73**, 550; (*d*) N. C. Giampietro and J. P. Wolfe, *J. Am. Chem. Soc.*, 2008, **130**, 12907; (*e*) V. Nair, A. T. Biju, K. Mohanan and E. Suresh, *Org. Lett.*, 2006, **8**, 2213; (*f*) Y. Ju and R. S. Varma, *J. Org. Chem.*, 2006, **71**, 135; (*g*) J. P. Waldo, S. Mehta and R. C. Larock, *J. Org. Chem.*, 2008, **73**, 6666.

5 (*a*) Z. Xie, X. Bian, X. Geng, S. Li and C. J. Wang, *Chem. Res.*, 2008, 52; (*b*) A. Lévai and J. Jekő, *J. Heterocyclic Chem.*, 2006, **43**, 1303 and references cited; (*c*) For an example in strongly basic conditions: D. G. Powers, D. S. Casebier, D. Fokas, W. J. Ryan, J. R. Troth and D. L. Coffen, *Tetrahedron*, 1998, **54**, 4085; (*d*) For alternative syntheses of 3,5-diarylpyrazolines, see references 2b and 4f–g.

6 For representative examples: U. Bauer, B. J. Egner, I. Nilsson and M. Berghult, *Tetrahedron Lett.*, 2000, **41**, 2713.
7 For the direct condensation of aroyl hydrazines: (*a*) S. A. Wadhal, K. N. Wadodkar and P. S. Pande, *Indian J. Heterocycl. Chem.*, 2005, **15**, 11; (*b*) S. S. Khan and A. Hasan, *Heterocycl. Comm.*, 2006, **12**, 377.
8 Representative examples: (*a*) P. Jagtap, A. Degterev, S. Choi, H. Keys, J. Yuan and G. D. Cuny, *J. Med. Chem.*, 2007, **50**, 1886; (*b*) F. Chimenti, E. Maccioni, D. Secci, A. Bolasco, P. Chimenti, A. Granese, O. Befani, P. Turini, S. Alcaro, F. Ortuso, R. Cirilli, F. La Torre, C. Cardia Maria and S. Distinto, *J. Med. Chem.*, 2005, **48**, 7113. For an improved method with K_2CO_3 under microwave irradiations:; V. M. Patel and K. Desai, *Arkivoc*, 2004, **i**, 123.
9 Reviews on hydrazines: (*a*) U. Ragnarsson, *Chem. Soc. Rev.*, 2001, **30**, 205; (*b*) E. Licandro and D. Perdicchia, *Eur. J. Org. Chem.*, 2004, 665.
10 Reviews on aza-Michael: (*a*) metallocatalysis: L.-W. Xu and C.-G. Xia, *Eur. J. Org,. Chem.*, 2005, 633. For organocatalysis, see: (*b*) J. L. Vicario, D. Badía and L. Carrillo, *Synthesis*, 2007, 2065; (*c*) D. Almaşi, D. A. Alonso and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 299.
11 Y. A. Al-Farkh, F. H. Al-Hajjar, F. S. Al-Shamali and H. S. Hamoud, *Chem. Pharm. Bull.*, 1979, **27**, 257.
12 (*a*) Special issue on organocatalysis: B. List, *Chem. Rev.*, 2007, **107**, 5413; (*b*) *Enantioselective Organocatalysis*; ed. P. I. Dalko, Ed.; Wiley-VCH: Weinheim, Germany, 2007.
13 For an interesting study on N^1/N^2 selectivity, see: A. E. Rosamilia, F. Aricò and P. Tundo, *J. Org. Chem.*, 2008, **73**, 1559.
14 For representative references: (*a*) Z. Wang, R. T. Skerlj and G. J. Bridger, *Tetrahedron Lett.*, 1999, **40**, 3543; (*b*) J. B. Arterburn, K. V. Rao, R. Ramdas and B. R. Dible, *Org. Lett.*, 2001, **3**, 1351; (*c*) M. Wolter, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 3803; (*d*) J. Barluenga, P. Moriel, F. Aznar and C. Valdés, *Org. Lett.*, 2007, **9**, 275; (*e*) M. S. Lam, H. W. Lee, A. S. C. Chan and F. Y. Kwong, *Tetrahedron Lett.*, 2008, **49**, 6192.
15 (*a*) M. P. Sibi and T. Soeta, *J. Am. Chem. Soc.*, 2007, **129**, 4522; (*b*) H. Yanagita and S. Kanemasa, *Heterocycles*, 2007, **71**, 699.
16 T. Ishikawa and T. Kumamoto, *Synthesis*, 2006, 737.
17 For recent references using TBD as a bifunctional catalyst, see: (*a*) W. Y. Ye, J. Xu, C.-T. Tan and C.-H. Tan, *Tetrahedron Lett.*, 2005, **46**, 6875; (*b*) C. Sabot, K. A. Kumar, C. Antheaume and C. Mioskowski, *J. Org. Chem.*, 2007, **72**, 5001; (*c*) A. Chuma, H. W. Horn, W. C. Swope, R. C. Pratt, L. Zhang, B. G. G. Lohmeijer, C. G. Wade, R. M. Waymouth, J. L. Hedrick and J. E. Rice, *J. Am. Chem. Soc.*, 2008, **130**, 6749; (*d*) R. Lee, X. Lim, T. Chen, G. K. Tan and C. H. Tan, *Tetrahedron Lett.*, 2009, **50**, 1560; (*e*) C. Ghobril, C. Sabot, C. Mioskowski and R. Baati, *Eur. J. Org. Chem.*, 2008, 4104 and references cited therein.
18 (*a*) D. J. Pasto and R. T. Taylor, *Org. React.*, 1991, **40**, 91; (*b*) M. H. Haukaas and G. O. O'Doherty, *Org. Lett.*, 2002, **4**, 1771.
19 For an elegant intramolecular version, see references 4c and 15b.
20 A cross-over experiment between the aza-Michael adduct **3a** and one equivalent of 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one **2k** (in acetonitrile at 60 °C for 24 h) led to a mixture of aza-Michael products **3a**/**3k** with 33% and 53% yields respectively. This shows the existence of an equilibrium between the aza-Michael adduct and acetylhydrazine even without amine base (see ESI† for details).
21 (*a*) pK_a of TBD, MTBD, TMG in acetonitrile (26.1, 25.4, 23.7 respectively): I. Kaljurand, A. Kütt, L. Sooväli, T. Rodima, V. Mäemats, I. Leito and I. A. Koppel, *J. Org. Chem.*, 2005, **70**, 1019; (*b*) B. Kovačević and Z. B. Maksić, *Org. Lett.*, 2001, **3**, 1523; (*c*) pK_a of TBD, MTBD in THF (21.7, 18.6 respectively): I. Kaljurand, T. Rodima, A. Pihl, V. Mäemets, I. Leito, I. A. Koppel and M. Mishima, *J. Org. Chem.*, 2003, **68**, 9988; (*d*) p*K*a of acetylhydrazine = 21.8 in DMSO: Y. Fu, L. Liu, R.-Q. Li, R. Liu and Q.-X. Guo, *J. Am. Chem. Soc.*, 2004, **126**, 814.
22 For a discussion comparing the deprotonation and the complexation role of a base in hydrazine alkylation, see reference 13.
23 The use of acetamide in similar reaction conditions did not furnished any product. A quite related α-effect was also found in organocatalysed aza-Michael process by alkoxyamine nucleophiles; for leading references, see: (*a*) Y. K. Chen, M. Yoshida and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 9328; (*b*) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao and A. Córdova, *Chem,. Commun.*, 2007, 849; (*c*) D. Pettersen, F. Piana, L. Bernardi, F. Fini, M. Fochi, V. Sgarzani and A. Ricci, *Tetrahedron Lett.*, 2007, **48**, 7805; (*d*) J. Lee, M.-H. Kim, S.-S. Jew, H.-G. Park and B.-S. Jeong, *Chem. Commun.*, 2008, 1932; (*e*) F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti and P. Melchiorre, *Angew. Chem., Int. Ed. Engl.*, 2008, **47**, 8703; (*f*) X. Lu and L. Deng, *Angew. Chem., Int. Ed. Engl.*, 2008, **47**, 7710.
24 C. G. Overberger and J.-P. Anselme, *J. Am. Chem. Soc*, 1964, **86**, 658.