DOI: 10.1002/chem.200801471

# Development, Scope and Mechanisms of Multicomponent Reactions of Asymmetric Electron-Deficient Alkynes with Amines and Formaldehyde

**Hua Cao, Xiujun Wang, Huanfeng Jiang,* Qiuhua Zhu, Min Zhang, and Haiyang Liu[a]**

*Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday*

**Abstract:** Based on the reactive behaviour of the substrates, two synthetic routes to polysubstituted pyrimidine derivatives are presented herein: 1) A catalyst-free multicomponent reaction of electron-deficient alkynes, aliphatic amines and formaldehyde and 2) $Ag^{I}$-catalyzed synthesis of pyrimidines from electron-deficient alkynes, anilines and formaldehyde by a domino reaction. Under optimized conditions, the multicomponent reactions were accomplished with high regioselectivity and excellent yields. A computational study was carried out by using the B3LYP density functional theory to elucidate the mechanisms of the catalyst-free hydroamination reaction. Calculations showed the activation free energies of aliphatic amines were lower than those of anilines, which is consistent with the experimental results.

**Keywords:** catalyst-free reactions · density functional calculations · multicomponent reactions · pyrimidines · silver catalyst

## Introduction

Multicomponent reactions (MCRs) are very attractive processes that push the limits of synthetic efficiency by using more than two reactants to create novel products with an optimal number of new bonds and functionalities.[1] The strategy of MCRs has been developed to enable the rapid construction of complex and diverse structures from readily accessible starting materials in a single operation under mild conditions.[2,3] Although the sequence of MCRs has been elegantly developed at the current stage of investigation in this field,[4] the multicomponent synthesis of heterocycles that are susceptible to further scaffold diversification and amplification is rare.[5] Some MCRs are catalyst-free, but most of these procedures usually need to be activated by a transition metal. Transition-metal-catalyzed MCRs have attracted considerable attention due to the fact that complicated organic molecules and drugs can be easily prepared from simple compounds in one reaction sequence.[6] Although a range of strategies involving the sequential generation of radical and anionic species have been used for such transformations,[7] relatively few transition-metal-catalyzed MCRs have been reported for the synthesis of complex cyclic compounds.[8] Thus, the development of new MCRs that allow assembly of polysubstituted heterocycles in a regioselective manner is in high demand.

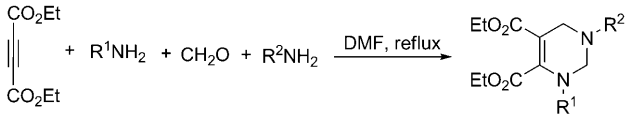
Pyrimidines are important chemicals that exhibit a wide range of biological activities.[9] Many naturally occurring compounds contain a pyrimidine skeleton as a key structural motif.[10] Because of the wide range of applications of pyrimidines in pharmaceutical research, such as muscarinic agonist activity,[11] protein–nucleic acid interactions,[12] antiviral activity[13] and inflammatory activity,[14] the development of efficient methods for their synthesis has continuously attracted the attention of many chemists. In modern organic synthesis, the hexahydropyrimidine nucleus has been employed as a protecting group in selective acylations and additions of 1,3-diamines owing to its easy cleavage in mildly acidic media.[15] Hexahydropyrimidines are classically prepared by condensation of substituted propane-1,3-diamines with aldehydes and ketones.[16–18] The convergent synthesis of these polysubstituted pyrimidine derivatives from readily available starting materials along this line also remains to be developed.[19,20]

[a] H. Cao, Prof. X. Wang, Prof. H. Jiang, Q. Zhu, M. Zhang, Prof. H. Liu
School of Chemistry and Chemical Engineering
South China University of Technology
Guangzhou 510640 (P.R. of China)
Fax: (+86) 20-87112906
E-mail: jianghf@scut.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801471.

Recently, we reported a convenient one-pot synthesis of polysubstituted tetrahydropyrimidines by catalyst-free MCRs (Scheme 1).[21] This process not only represents a




Scheme 1. One-pot synthesis of polysubstituted tetrahydropyrimidines by a catalyst-free MCR. DMF = dimethylformamide.

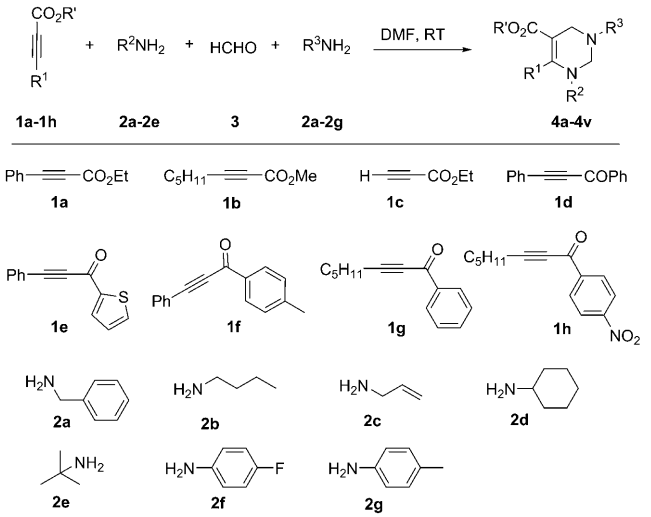
convenient procedure for the clean synthesis of polysubstituted pyrimidines, but also opens up a potential route for the preparation of other polysubstituted heterocycles.[22] In our further exploration of the scope of this novel domino reaction, we employed ethyl phenylpropiolate as the substrate and surprisingly found that aliphatic amines can finish the MCRs smoothly but that anilines cannot under the same conditions, which is quite different from the result obtained by using the electron-withdrawing alkyne diethyl acetylenedicarboxylate.[21] In the process of this research, we explored the reactive behaviour of different kinds of starting materials, the addition selectivity of amines to the carbon–carbon triple bond and the order of the domino sequences. With the goal of broadening the utility of MCR methodology in organic synthesis, we are interested in studying the reactive behaviour of the substrates, exploring the key step in domino sequences and understanding the mechanisms of the processes in detail.

In recent computational studies, the mechanism of hydroamination reactions in a catalytic system has been investigated,[22] which will be helpful in understanding a multitude of steps in our MCRs. Herein, we report the development of effective procedures for the MCRs of asymmetric electron-deficient alkynes, amines and formaldehyde, and the mechanistic investigation of all steps in the both the catalyst-free and catalytic cycle MCRs by using a combination of the B3LYP density functional theory (DFT) and experimental methods.

## Results and Discussion

**MCRs and their regioselectivity under catalyst-free conditions**: At the beginning of this study, we found that asymmetric ethyl phenylpropiolate (**1a**) could react smoothly with benzylamine (**2a**) and formaldehyde under catalyst-free conditions at room temperature for 6 h. The isolated product (**4a**) was obtained in 89% yield (Table 1, entry 1). Besides the analytical results of $^{1}H$ and $^{13}C$ NMR spectra, the intermediate product (Scheme 2), which has been identified by X-ray crystallography (Figure 1), showed that the reaction was carried out with high regioselectivity and only gave the Markovnikov addition product. In addition, similar

Table 1. One-pot synthesis of polyfunctional tetrahydropyrimidines by a catalyst-free MCR.[a]



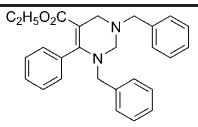
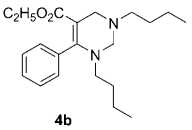
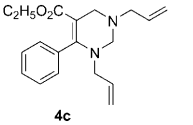
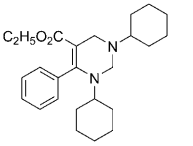
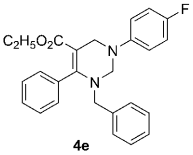
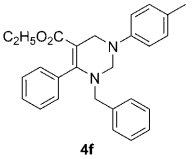
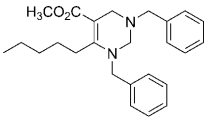

| | Alkynoate | $R^2NH_2$ | $R^3NH_2$ | *t* [h] | Product | Yield[b] [%] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | | 6 |  **4a** | 89 |
| 2 | **1a** | **2b** | | 8 |  **4b** | 90 |
| 3 | **1a** | **2c** | | 6 |  **4c** | 90 |
| 4 | **1a** | **2d** | | 8 |  **4d** | 89 |
| 5[c] | **1a** | **2a** | **2f** | 6 |  **4e** | 81 |
| 6[c] | **1a** | **2a** | **2g** | 6 |  **4f** | 80 |
| 7 | **1a** | **2f** | **2a** | 14 | n.d.[d] | – |
| 8 | **1a** | **2g** | **2a** | 14 | n.d. | – |
| 9 | **1b** | **2a** | | 5 |  **4g** | 88 |

Table 1. (Continued)

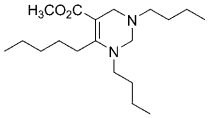
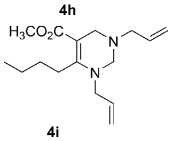
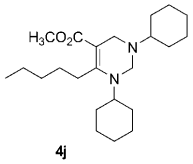
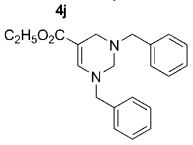
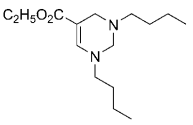
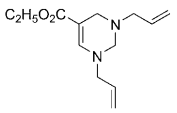
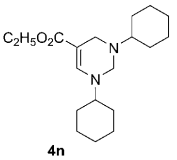
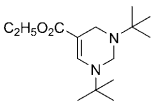
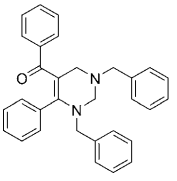
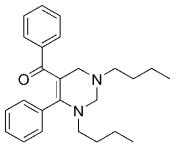
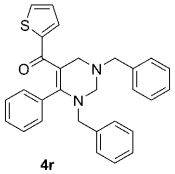
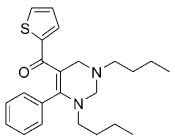
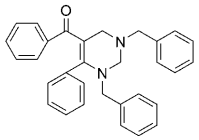
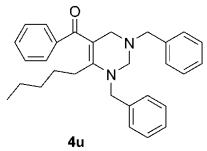
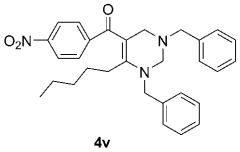
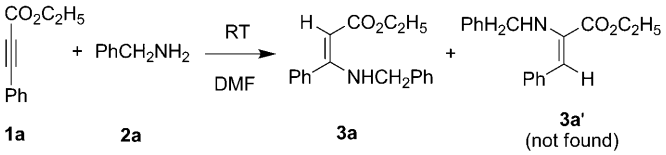
| | Alkynoate | $R^2NH_2$ | $R^3NH_2$ | *t* [h] | Product | Yield[b] [%] |
|---|---|---|---|---|---|---|
| 10 | **1b** | | **2b** | 5 |  **4h** | 89 |
| 11 | **1b** | | **2c** | 5 |  **4i** | 88 |
| 12 | **1b** | | **2d** | 5 |  **4j** | 87 |
| 13 | **1c** | | **2a** | 2.5 |  **4k** | 93 |
| 14 | **1c** | | **2b** | 2.5 |  **4l** | 93 |
| 15 | **1c** | | **2c** | 2.5 |  **4m** | 92 |
| 16 | **1c** | | **2d** | 2.5 |  **4n** | 92 |
| 17 | **1c** | | **2e** | 3 |  **4o** | 90 |
| 18 | **1d** | | **2a** | 5 |  **4p** | 87 |
| 19 | **1d** | | **2b** | 5 |  **4q** | 91 |

Table 1. (Continued)

| | Alkynoate | $R^2NH_2$ | $R^3NH_2$ | *t* [h] | Product | Yield[b] [%] |
|---|---|---|---|---|---|---|
| 20 | **1e** | | **1a** | 5 |  **4r** | 86 |
| 21 | **1e** | | **1b** | 5 |  **4s** | 86 |
| 22 | **1f** | | **1a** | 5 |  **4t** | 90 |
| 23 | **1g** | | **1a** | 5 |  **4u** | 85 |
| 24 | **1h** | | **1a** | 5 |  **4v** | 85 |

[a] Reaction conditions unless stated otherwise: alkynoate (1.0 mmol), aliphatic amine (2.2 mmol), formaldehyde (4.0 mmol), RT. [b] Isolated yields. [c] Reaction conditions: ethyl phenylpropiolate (1.1 mmol), phenylmethanamine (1 mmol), anilines (1.2 mmol), formaldehyde (4.0 mmol), RT. [d] n.d. = not detected.




Scheme 2. Hydroamination of benzylamine with ethyl phenylpropiolate.

desired products **4b–d** could be formed in good yields if **2b–d** were substituted for benzylamine (Table 1, entries 2–4).

When two different amines were employed in this reaction, an interesting phenomenon was observed (Table 1, entries 5, 6). The reaction proceeded smoothly and resulted in good yields if **2a** was added first. In contrast, no desired products were detected if aromatic amine **2f** or **2g** was added first (Table 1, entries 7, 8); however, the fact that **4e** and **4f** are obtained from the former reaction indicates that hydroamination between **1a** and **2a** cannot take place. When **1a** was replaced by methyl oct-2-ynoate (**1b**) or ethyl propiolate (**1c**) in this MCR, we found that a range of sub-

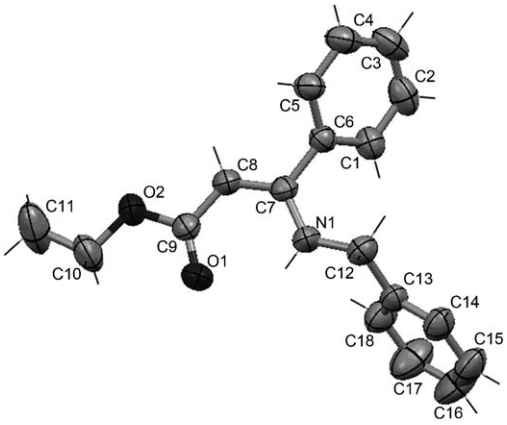
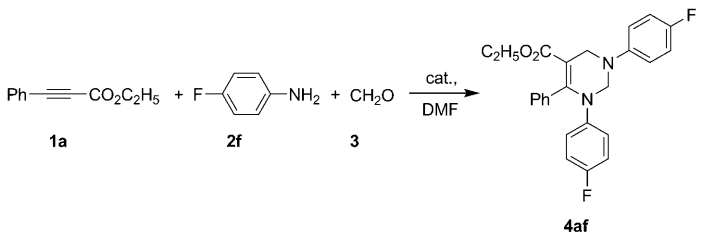



Figure 1. X-ray structures of **3a**. Ellipses are drawn at the 40% probability level.

stitutions on the aliphatic amines were well tolerated under our conditions, and the isolated yields obtained for **4g–o** varied from 87 to 93% (Table 1, entries 9–17). Interestingly, the reaction of **1c** with aliphatic amines and formaldehyde is more effective and the reaction time was dramatically reduced to 2.5–3 h (Table 1, entries 13–17). In addition, sterically hindered substituted amines, such as *tert*-butylamine (**2e**), also gave high yields (**4o**; Table 1, entry 17). It is worth mentioning that all the desired products were formed with high regioselectivity in our experiments.

**MCRs and their regioselectivity under catalytic conditions**: When aromatic substituted amines were employed as the substrates in the MCRs of **1a** under catalyst-free conditions, we found that the desired products were not observed even after 14 h at room temperature (Table 2, entries 7, 8). Further examination showed that domino sequences were impeded at the hydroamination step (Table 1, entries 5, 6). Considering that hydroamination is the triggering sequence, we then focused our effort on the search for a catalyst to promote the hydroamination step and complete the transformation. The transition-metal catalysts emerged as the preferred choice because they have been proven to be the most powerful and useful tools for hydroamination reactions.[23] More good processes that use early- and late-transition-metal catalysts have recently been developed. In general, the advantage of late-transition-metal catalysts is their greater tolerance of polar functional groups. The first successful demonstration of this process was with $Rh^{III}$[24] and $Ir^{III}$[25] complexes. More recently, $Ru_3(CO)_{12}$[26,27] and [Rh(cod)$_2$]$BF_4$[28] (cod = cyclooctadiene) have been applied to the catalytic intermolecular hydroamination of aniline derivatives and terminal alkynes. Therefore, we still chose ethyl phenylpropiolate, 4-fluoroaniline and formaldehyde as the standard substrates to search for potential catalysts and suitable reaction conditions. We first examined the reaction in the presence of 3 mol% $AuCl_3$. Although the hydroamination step proceeded, the desired product, **4af**, was obtained in only 8% yield after stirring at 100°C in DMF for 14 h (Table 2, entry 1). If other late-transition-metal catalysts,

Table 2. Catalyst and temperature screening results.[a]




| | Catalyst | Additive | $T$ [°C] | $t$ [h] | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | $AuCl_3$ | – | 100 | 14 | 8 |
| 2 | $PdCl_2$ | – | 100 | 14 | – |
| 3 | $Pd(NO_3)_2$ | – | 100 | 14 | – |
| 4 | AgOAc | – | 100 | 14 | 30 |
| 5 | AgOAc | – | 50 | 14 | 31 |
| 6 | AgOAc | – | RT | 14 | 35 |
| 7 | $AgBF_4$ | – | RT | 14 | 40 |
| 8 | $AgBF_4$ | L-proline | RT | 6 | 80 |
| 9 | $AgBF_4$ | $PPh_3$ | RT | 6 | 30 |
| 10 | $AgBF_4$ | $Et_3N$ | RT | 6 | 10 |
| 11 | $AgBF_4$ | $t$BuNH$_2$ | RT | 6 | 27 |
| 12 | AgOAc | DABCO[c] | RT | 6 | 13 |
| 13 | $Ag_2CO_3$ | L-proline | RT | 10 | 20 |
| 14 | $AgNO_3$ | L-proline | RT | 10 | 37 |
| 15 | $Ru_3(CO)_{12}$ | L-proline | RT | 10 | 35 |
| 16 | $AuCl_3$ | – | 100 | 14 | 8 |

[a] Reaction conditions: alkynoate (1.0 mmol), anlines (2.2 mmol), formaldehyde (3.5 mmol), RT. [b] Isolated yields. [c] DABCO = 1,4-diazabicyclo[2.2.2]octane.

such as $PdCl_2$ (Table 2, entry 2) and $Pd(NO_3)_2$ (Table 2, entry 3), were employed, no conversion was observed, as indicated by the complete recovery of ethyl phenylpropiolate and aniline. These results clearly indicate that an appropriate transition-metal catalyst for this domino reaction should not only serve as a good catalyst to complete the hydroamination step in high yield and regioselectivity, but should also promote sequences such as Mannich-type reactions and dehydration–cyclization. After much effort, we were delighted to find that MCRs gave the desired product in 30% yield at 100°C for 14 h with AgOAc as the catalyst (Table 2, entry 4), and to our pleasure AgOAc could catalyze MCRs even at room temperature (Table 2, entry 6). The experimental results showed that Ag catalysts are a good choice for these domino sequences. After a series of further optimizations, $AgBF_4$/L-proline was chosen as the most effective catalyst (Table 2, entries 7–12). In the presence of 5 mol% $AgBF_4$ and 5 mol% L-proline, the desired product can be obtained in 80% yield at room temperature and the reaction time was dramatically reduced to 6 h (Table 2, entry 8). Other catalysts, such as $Ag_2CO_3$, $AgNO_3$ and $Ru_3(CO)_{12}$, were employed in the reaction but only led to moderate yields of product (Table 2, entries 13–15). Different solvents were also examined and excellent results were obtained by using DMF.

With $AgBF_4$/L-proline as a suitable catalytic system, we then attempted to improve the yield by adjusting the ratio of the reactants (Table 3). The reaction proceeded in DMF with $AgBF_4$/L-proline as the catalyst. The amount of **1a** was

Table 3. Screening results for the best ratio of the three reactants.

| | Alkynonate [mmol] | 4-Fluoroaniline [mmol] | Formaldehyde [mmol] | Yield[a] [%] |
|---|---|---|---|---|
| 1 | 1.0 | 2.0 | 2.5 | 68 |
| 2 | 1.0 | 2.0 | 3.0 | 71 |
| 3 | 1.0 | 2.0 | 3.5 | 73 |
| 4 | 1.0 | 2.0 | 4.0 | 76 |
| 5 | 1.0 | 2.0 | 4.5 | 75 |
| 6 | 1.0 | 2.0 | 5.0 | 70 |
| 7 | 1.0 | 2.1 | 4.0 | 75 |
| 8 | 1.0 | 2.2 | 4.0 | 77 |
| 9 | 1.0 | 2.3 | 4.0 | 80 |
| 10 | 1.0 | 2.4 | 4.0 | 82 |
| 11 | 1.0 | 2.5 | 4.0 | 81 |
| 12 | 1.0 | 3.0 | 4.0 | 76 |

[a] Isolated yields.

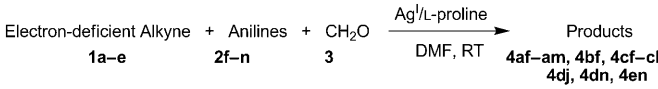
fixed to 1 mmol. When the amounts of 4-fluoroaniline and formaldehyde were increased, the yield of the desired product increased until the ratio of **1a**, 4-fluoroaniline and formaldehyde reached 1:2.4:4 (Table 3, entry 10).

On the basis of the above experiments, we chose the following optimized reaction conditions: 5 mol% $AgBF_4$ and 5 mol% L-proline as the catalyst and electron-deficient alkyne, anilines and formaldehyde in a ratio of 1:2.4:4 in DMF stirred at room temperature for an appropriate time. The results are summarized in Table 4.

From Table 4, we found that the reaction conditions proved to be useful for alkenes **1a–c**, inert anilines (**2f–k**) and formaldehyde, and the MCRs usually went to completion in 2.5–6 h. For the reaction of ethyl phenylpropiolate (**1a**), **2f–m** and formaldehyde, both electron-rich and electron-poor anilines, which are suitable partners in this process, gave good yields (**4af–al**; Table 4, entries 1–8). Of the various substituted amines, 4-fluoroaniline (**2f**), 4-chloroamiline (**2h**) and 4-bromoamiline (**2i**; Table 4, entries 1, 3, 4) reacted more smoothly with **1a** in the presence of the $AgBF_4$/L-proline catalytic system. This indicates that nearly all the anilines that have different substituent groups on the aromatic ring could react smoothly, and the resulting corresponding products were obtained in good yields. Interestingly, sterically hindered substituted amines, such as 2-methylaniline (**2m**), also gave high yields, which infers that groups around the -$NH_2$ group do not affect the reactivity of the amine (Table 4, entry 8). When **1a** was replaced by **1b** or **1c** in this reaction, we found that a range of substitutions on the anilines was well tolerated under optimum conditions (**4bm–ck**; Table 4, entries 9–15). The molecular structure of representative product **4af** was determined by X-ray crystallography (Figure 2). It was proven that regioselective products have been obtained in our study.

**The stereoselectivity of the hydroamination step**: In this domino sequence, the hydroamination of **1a** with amines is the key step. To gain further insight into the stereoselectivity of the catalyst-free and $Ag^I$-catalyzed hydroamination processes and the nature of the observed high *cis* selectivity, we carried out a series of reactions with electron-deficient alkynes. The configuration of the enamino double bond in

Table 4. $AgBF_4$/L-proline-catalyzed MCRs of asymmetric electron-deficient alkynes, anilines and formaldehyde.[a]



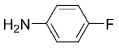
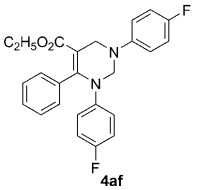
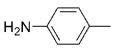
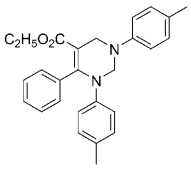
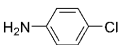
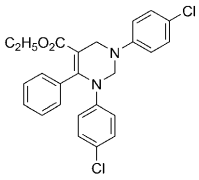
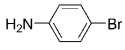
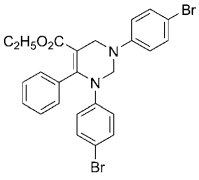
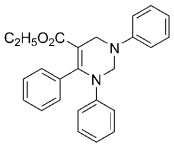
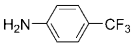
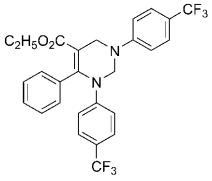
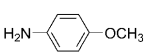
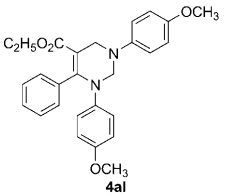

| | Electron-deficient alkyne | Aromatic amine | *t* [h] | Product | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | **1a** |  **2f** | 6 |  **4af** | 83 |
| 2 | **1a** |  **2g** | 6 |  **4ag** | 80 |
| 3 | **1a** |  **2h** | 6 |  **4ah** | 82 |
| 4 | **1a** |  **2i** | 6 |  **4ai** | 81 |
| 5 | **1a** |  **2j** | 5 |  **4aj** | 80 |
| 6 | **1a** |  **2k** | 5 |  **4ak** | 81 |
| 7 | **1a** |  **2l** | 6 |  **4al** | 78 |

Table 4. (Continued)

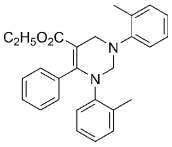
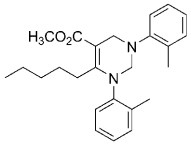
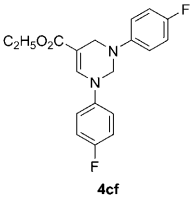
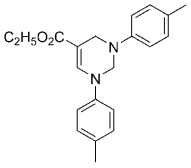
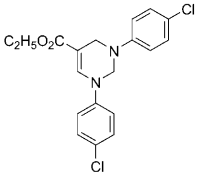
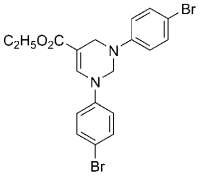
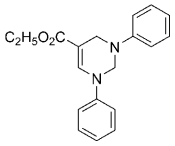
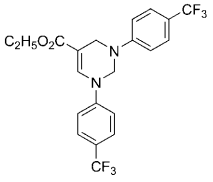
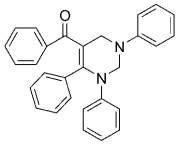
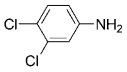
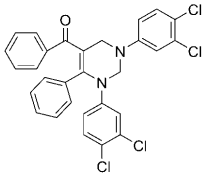
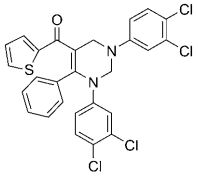
| | Electron-deficient alkyne | Aromatic amine | *t* [h] | Product | Yield[b] [%] |
|---|---|---|---|---|---|
| 8 | **1a** |  **2m** | 5 |  **4am** | 80 |
| 9 | **1b** | **2m** | 6 |  **4bm** | 72 |
| 10 | **1c** | **2f** | 2.5 |  **4cf** | 85 |
| 11 | **1c** | **2g** | 2.5 |  **4cg** | 85 |
| 12 | **1c** | **2h** | 2.5 |  **4ch** | 86 |
| 13 | **1c** | **2i** | 2.5 |  **4ci** | 83 |
| 14 | **1c** | **2j** | 2.5 |  **4cj** | 84 |
| 15 | **1c** | **2k** | 2.5 |  **4ck** | 81 |

Table 4. (Continued)

| | Electron-deficient alkyne | Aromatic amine | *t* [h] | Product | Yield[b] [%] |
|---|---|---|---|---|---|
| 16 | **1d** | **2j** | 5 |  **4dj** | 82 |
| 17 | **1d** |  **2n** | 5 |  **4do** | 79 |
| 18 | **1e** | **2n** | 5 |  **4eo** | 84 |

[a] Reaction conditions: electron-deficient alkyne (1.0 mmol), anilines (2.4 mmol), formaldehyde (4.0 mmol), RT. [b] Isolated yields.

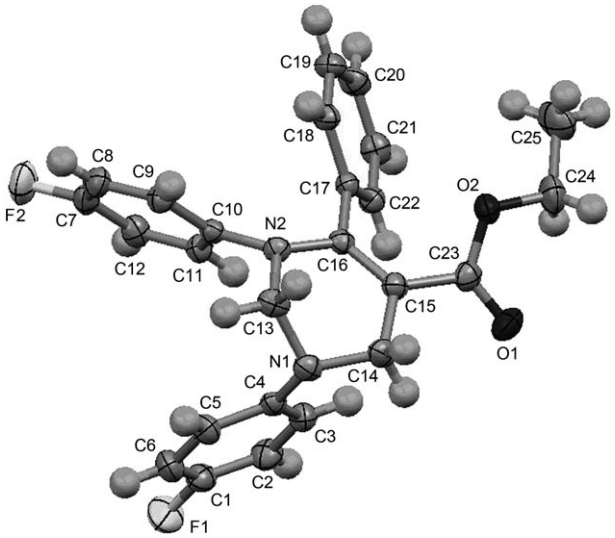
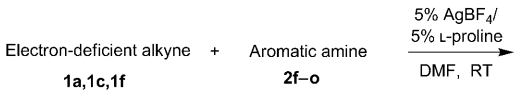


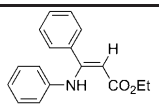
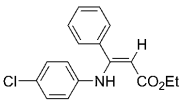
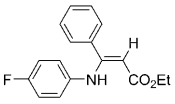
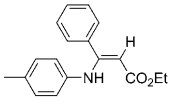
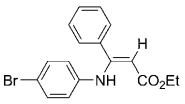
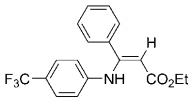
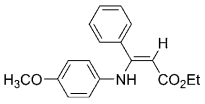
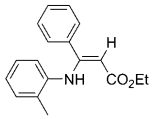
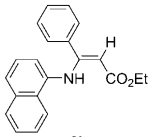
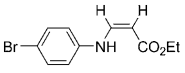
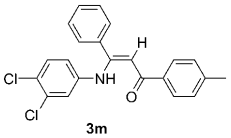

Figure 2. X-ray structure of **4af**. Ellipses are drawn at the 32% probability level.

products **3a** and **3c–n** (Table 5) was identified by $^{1}$H and $^{13}$C NMR spectroscopy. The molecular structures of representative product **3a** (Figure 1) and **3d** (Figure 3) were determined by X-ray crystallography. The downfield chemical shift of the N–H proton ($\delta > 8$ ppm) is a typical feature of a hydrogen bond with oxygen in a carbonyl group, which indicates a chelated *Z* configuration. We believe that this reaction proceeds via intermediate **3b**, which contains both a

Table 5. $AgBF_4$/L-proline-catalyzed hydroamination of electron-deficient alkynes with anilines.[a]




| | Electron-deficient alkyne | Aromatic amine | $t$ [h] | Product | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | **1a** | **2j** | 5 |  **3c** | 85 |
| 2 | **1a** | **2h** | 5 |  **3d** | 82 |
| 3 | **1a** | **2f** | 5 |  **3e** | 82 |
| 4 | **1a** | **2g** | 5 |  **3f** | 81 |
| 5 | **1a** | **2i** | 5 |  **3g** | 84 |
| 6 | **1a** | **2k** | 5 |  **3h** | 81 |
| 7 | **1a** | **2l** | 5 |  **3i** | 83 |
| 8 | **1a** | **2m** | 5 |  **3j** | 84 |
| 9 | **1a** |  **2o** | 5 |  **3k** | 80 |
| 10 | **1c** | **2i** | 5 |  **3l** | 86 |
| 11 | **1f** | **2n** | 5 |  **3m** | 85 |

[a] Reaction conditions: electron-deficient alkyne (1.0 mmol), anlines (2.4 mmol), RT. [b] Isolated yields.

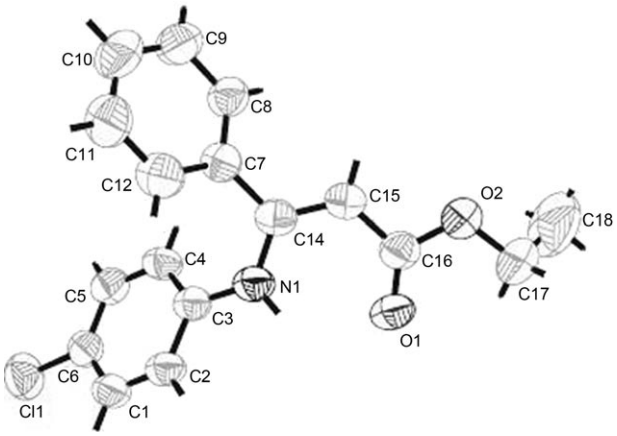


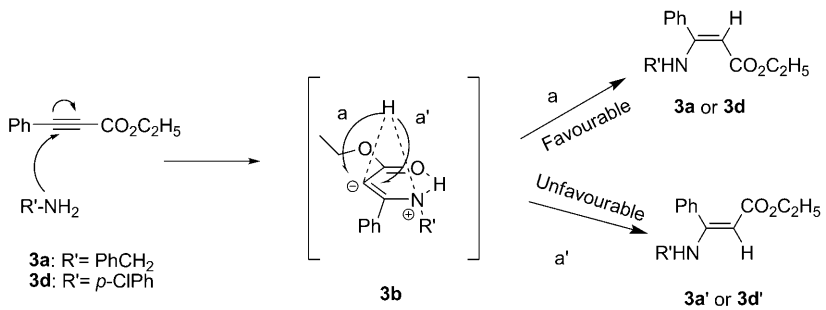

Figure 3. X-ray structure of **3d**. Ellipses are drawn at the 62% probability level.

six- and a four-membered ring (Scheme 3). This explains the high *cis* selectivity of the hydroamination process well.[29] High stereoselectivity was obtained due to the formation of a hydrogen bond[30] that stabilizes **3b**. From **3b**, there are two possible routes a and a′ to form **3d** and **3d′**, respectively. It is obvious that route a is the favourable one due to the lower steric hindrance and the formation of a hydrogen bond that stabilizes **3b**.

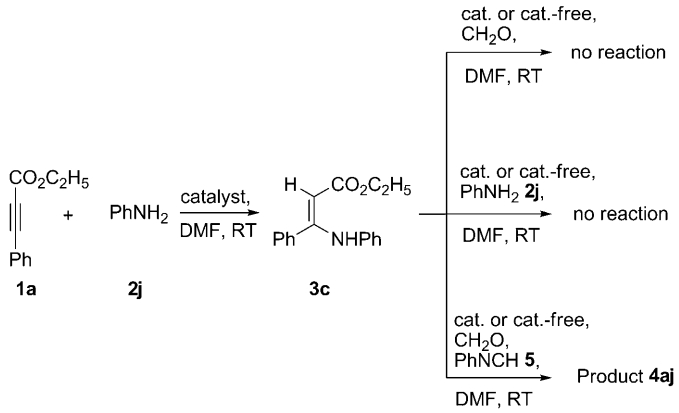
**Mechanism**: In an effort to understand why and how these MCRs could be carried out under catalyst-free and catalytic conditions, a mechanistic study of the MCRs was undertaken by using a combination of experimental and theoretical methods. Experimental work on the hydroamination reaction of asymmetric electron-deficient alkynes proved the regioselectivity by verifying two possible structures of the products (Scheme 2). A computational study was carried out by using ab initio calculations to elucidate the activation free energy of the substrates.

In the regiochemistry of asymmetric electron-deficient alkynes, the addition reaction of amine to a carbon–carbon triple bond is highly regioselective due to the nucleophilic attack by the nitrogen atom of the amine. Our study demonstrates that both the catalyst-free and the Ag-catalyzed processes stereoselectively promote the *cis*-selective hydroamination of ethyl phenylpropiolate with amines. Therefore, the Ag-catalyzed process is an example to describe the detailed mechanism of this domino sequence. To study the order of the domino sequences, three experiments were performed as shown in Scheme 4. First, we prepared intermediate product **3c**, which was determined by GCMS under $AgBF_4$/L-proline catalytic conditions. The reactions of **3c** with formaldehyde and with aniline were retarded under both catalyst and catalyst-free conditions after stirring at room temperature in DMF. However, the desired product (**4aj**) was obtained after **3c**, formaldehyde and *N*-methyleneaniline (**5**) were stirred at room temperature in DMF. This result suggests that the order of this domino reaction is hydroamination, a Mannich-type reaction and then dehydration–cyclization.

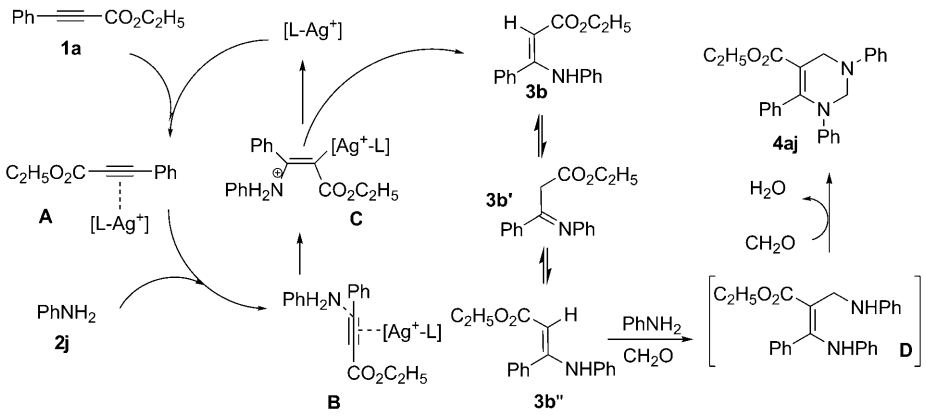



Scheme 3. Two possible routes for the formation of enamino intermediates.




Scheme 4. Examination of the MCR mechanism by studying the reactions of **3c** under different conditions.

On the basis of these results, we depict a possible mechanism in Scheme 5. **1a** is activated by [Ag/proline]$^+$ to generate the cationic Ag$^I$–alkyne complex **A**, followed by coordination of aniline to the Ag centre (**B**). The coordination of $AgBF_4$ to alkynoates lowers the electron density of the carbon–carbon triple bond, which makes the nucleophilic attack of anilines toward alkynoates easier and smoother. Intermediate **B** further undergoes C–N bond formation to give polarized intermediate **C** prior to the formation of hydroaminating adduct **3c**. Subsequently, compound **D** was formed by a Mannich-type reaction of **3c** and **5**. Finally, with the addition of formaldehyde, **4aj** was obtained via dehydration–cyclisation.




Scheme 5. Proposed mechanism for $AgBF_4$/L-proline-catalyzed MCRs. L = L-proline.

**DFT calculations**: From the mechanistic study, it can be seen that the hydroamination reaction is the rate-determining step in the MCRs. A computational study was carried out by using ab initio calculations to elucidate the activation free energy of the substrates. DFT was used to elucidate the mechanism of the catalyst-free hydroamination reaction of **1a**, **1b**, **1c** and diethyl acetylenedicarboxylate (**1i**) with **2j** or **2a**. All calculations were carried out by using the Gaussian 03 programs.[31] The geometrical optimizations of all intermediates and transition states were performed by using Becke's three-parameter exchange functional and the non-local correlation functional of Lee, Yang and Parr[32] (B3LYP) with the 6–31G(d) basis set for all atoms. Frequency calculations at the same level were performed to confirm each stationary point as either a minimum or a transition structure (TS). In the following discussion, the energies are relative Gibbs free energies ($\Delta G_{298}$).

The DFT-computed energy surface in the gas phase for the hydroamination reaction between **1i** with **2a** or **2j** is given in Figure 4. The activation free energy $\Delta G$ for **2j** is given in brackets. The first step of hydroamination reaction starts with a nucleophilic addition of **2j** or **2a** to the triple bond of **1i** (Figure 4). Complex **S1** has a carbine atom in its structure. The calculations indicate that the singlet state of **S1** is much more stable than the triplet state. $\Delta G_0$ are the activation free energy of the nucleophilic addition reactions. The conversion from **S1** to intermediate **S2** via a four-membered-ring transition structure is a [1,3]-hydrogen shift process with an activation free energy of $\Delta G_1$. The four-membered ring is composed of ethynyl, nitrogen and hydrogen atoms. $\Delta G_s$, the sum of $\Delta G_0$ and $\Delta G_1$, is the activation free energy of the catalyst-free hydroamination reaction. $\Delta G_2$ is the activation free energy of the reverse reaction for this step. During the second step, intermediate **S2** transforms via transition structure **TS2** into product **S3**, which is much more thermodynamically stable. The activation free energy of the second step is $\Delta G_3$. Because the absolute value of $\Delta G_3$ is smaller than that of $\Delta G_2$, the second reaction proceeds smoothly. Consequently, the whole reaction is a kinetically controlled process. The values of $\Delta G_0$, $\Delta G_1$ and

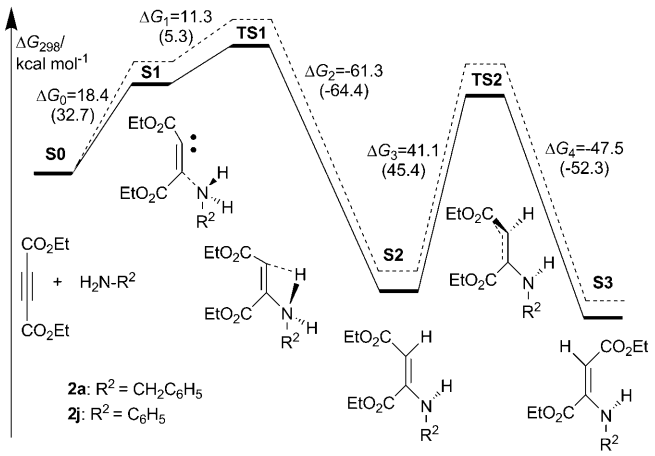



Figure 4. DFT-computed energy surfaces for the catalyst-free hydroamination reactions between **1i** with **2a** or **2j**.

$\Delta G_2$ for different reactions are listed in Table 6. From Table 6, all $\Delta G$ values for benzylamine (**2a**) were lower than those for aniline (**2j**). Therefore, the hydroamination reaction of benzylamine (**2a**) should be faster than that of aniline (**2j**), which is consistent with our experimental results. In our experiments, all the hydroamination reactions of **2a** and the reaction between **1i** with **2j** can easily proceed even under catalyst-free conditions. As a result, we believe that $\Delta G = 41$ kcal mol$^{-1}$ may be the threshold activation free energy. If the activation free energy is lower than this threshold energy, the hydroamination reactions can proceed under catalyst-free conditions, whereas if the activation energy is higher than 41 kcal mol$^{-1}$, the hydroamination reaction can only be performed with the aid of a suitable catalyst.

Table 6. The computed Gibbs free energies [kcal mol$^{-1}$] for the hydroamination reactions.

| Reactants | | $\Delta G_0$ | $\Delta G_1$ | $\Delta G_s$ | $\Delta G_2$ |
|---|---|---|---|---|---|
| **1a** | **2a** | 44.9 | 3.0 | 47.9 | −66.7 |
| | **2j** | 35.3 | 5.5 | 40.8 | −62.9 |
| **1b** | **2a** | 43.2 | 4.1 | 47.3 | −70.9 |
| | **2j** | 35.5 | 4.9 | 40.4 | -63.5 |
| **1c** | **2a** | 37.0 | 4.7 | 41.7 | −78.7 |
| | **2j** | 28.4 | 6.8 | 35.2 | −72.6 |
| **1i** | **2a** | 32.7 | 5.3 | 38.0 | −64.4 |
| | **2j** | 18.4 | 11.3 | 29.7 | −58.4 |

## Conclusion

In summary, we have reported two novel multicomponent reactions that lead to polysubstituted pyrimidine starting from simple and readily available inputs. The reactions are highly regioselective in that only the Markovnikov addition product is observed and no anti-Markovnikov product was formed. DFT calculations show the activation free energies for aliphatic amines were lower than those for anilines, which is consistent with the experimental results. Furthermore, the good product yields, mild reaction conditions and use of simple starting materials are the main advantages of this method.

## Experimental Section

**General methods**: All reactions were performed at RT under air in a round bottom flask equipped with a magnetic stir bar. $^1$H and $^{13}$H NMR spectra were recorded by using a Bruker Avance 400 MHz NMR spectrometer and referenced to $\delta = 7.24$ and 77.0 ppm for chloroform with TMS as the internal standard. IR spectra were obtained as potassium bromide pellets or as liquid films between two potassium bromide pellets by using a Brucker Vector 22 spectrometer. Mass spectra were recorded by using a Shimadzu GCMS-QP5050 A instrument set at an ionization voltage of 70 eV and equipped with a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m). Elemental analysis was performed by using a Vario EL elemental analyzer. TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF254), and visualization was performed at 254 nm and 365 nm. All chemicals were purchased from Aldrich Chemicals.

CCDC-706544 (**3a**), -706546 (**4af**) and -706545 (**3d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**General procedure for the synthesis of ethyl 1,3-dibenzyl-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate four-component reactions**: Benzylamine (2.2 mmol) and DMF (3 mL) were successively added with stirring to ethyl phenylpropiolate (1 mmol). The mixture was stirred at RT for 6 h, then formaldehyde (4 mmol) was added. After completion of the reaction (as monitored by TLC), the solution was evaporated to dryness under reduced pressure and then water (8 mL) was added. The aqueous solution was extracted with diethyl ether (3 × 15 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by column chromatography to give a pure sample of ethyl 1,3-dibenzyl-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**).

**General procedure for the synthesis of ethyl 1,3,6-triphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate by three-component reactions**: Aniline (2.4 mmol), $AgBF_4$ (5 mol %), L-proline (5 mol %) and DMF (3 mL) were successively added with stirring to ethyl phenylpropiolate (1 mmol). The mixture was stirred at RT for 5 h, then formaldehyde (4 mmol) was added. After completion of the reaction (as monitored by TLC), the solution was evaporated to dryness under reduced pressure and then water (8 mL) was added. The aqueous solution was extracted with diethyl ether (3 × 15 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by column chromatography to give a pure sample of ethyl 1,3,6-triphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4af**).

## Acknowledgements

We thank the National Natural Foundation of China (Nos. 20332030, 20572027, 20625205 and 20772034) and Guangdong Natural Science Foundation (No. 07118070) for financial support.

[1] *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**.

[2] a) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind.* **1997**, 23, 765–767; d) S. L. Schreiber, *Science* **2000**, *287*, 1964–1966;

e) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.

[3] a) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–53; b) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; c) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957–4980; d) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; e) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628–1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; f) D. Enders, C. Grondal, M. R. M. Huttl, *Angew. Chem.* **2007**, *119*, 1567; *Angew. Chem. Int. Ed.* **2007**, *46*, 1545; g) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899–907.

[4] a) T. A. Keating, R. W. Armstrong, *J. Am. Chem. Soc.* **1996**, *118*, 2574–2583; b) T. A. Keating, R. W. Armstrong, *J. Org. Chem.* **1996**, *61*, 8935–8939; c) C. Hulme, J. Peng, S. Y. Tang, C. J. Burns, I. Morize, R. Labaudiniere, *J. Org. Chem.* **1998**, *63*, 8021–8023; d) D. Fokas, W. J. Ryan, D. S. Casebier, D. G. Coffen, *Tetrahedron Lett.* **1998**, *39*, 2235–2238; e) C. Hulme, M. P. Cherrier, *Tetrahedron Lett.* **1999**, *40*, 5295–5299; f) H. Wang, A. Ganesan, *Org. Lett.* **1999**, *1*, 1647–1649; g) H. Bienayme, K. Bouzid, *Tetrahedron Lett.* **1999**, *40*, 2735–2738; h) K. Paulvannan, *Tetrahedron Lett.* **1999**, *40*, 1851–1854; i) K. Paulvannan, J. W. Jacobs, *Tetrahedron* **1999**, *55*, 7433–7440; j) C. Hulme, L. Ma, M. P. Cherrier, J. J. Romano, G. Morton, C. Duquenne, J. Salvino, R. Labaudiniere, *Tetrahedron Lett.* **2000**, *41*, 1883–1887; k) J. Quiroga, C. Cisneros, B. Insuasty, R. Aboniá, M. Nogueras, A. Sánchez, *Tetrahedron Lett.* **2001**, *42*, 5625–5627; l) B. Beck, M. Magnin-Lachaux, E. Herdtweck, A. Dömling, *Org. Lett.* **2001**, *3*, 2875–2878.

[5] D. Lee, J. K. Sello, S. L. Schreiber, *J. Am. Chem. Soc.* **1999**, *121*, 10648–10649.

[6] a) J. C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; b) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302–312; c) J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, New York, **2002**; d) S. I. Ikeda, *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 960–963; e) J. Montgomery, *Acc. Chem. Res.* **2000**, *33*, 467–473; f) S. I. Ikeda, *Acc. Chem. Res.* **2000**, *33*, 511–519; g) L. S. Hegedus, *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed., University Science Books, Sausalito (USA), **1999**; h) E. Negishi, C. Coperet, S. Ma, S. H. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365–394; i) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; j) R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103–13159; k) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163.

[7] a) K. Tsuchii, M. Doi, T. Hirao, A. Ogawa, *Angew. Chem.* **2003**, *115*, 3614–3617; *Angew. Chem. Int. Ed.* **2003**, *42*, 3490–3493; b) K. Takai, N. Matsukawa, A. Takahashi, T. Fujii, *Angew. Chem.* **1998**, *110*, 160–163; *Angew. Chem. Int. Ed.* **1998**, *37*, 152–155; c) J. Terao, K. Saito, S. Nii, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1998**, *120*, 11822–11823; d) K. Takai, T. Ueda, N. Ikeda, T. Moriwake, *J. Org. Chem.* **1996**, *61*, 7990–7991; e) I. Ryu, H. Yamazaki, A. Ogawa, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1993**, *115*, 1187–1189; f) T. Shono, I. Nishiguchi, M. Sasaki, *J. Am. Chem. Soc.* **1978**, *100*, 4314–4315.

[8] a) K. Inanaga, K. Takasu, M. Ihara, *J. Am. Chem. Soc.* **2004**, *126*, 1352–1353; b) A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842–3848; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754–3760; c) P. A. Wender, G. G. Gamber, M. J. C. Scanio, *Angew. Chem.* **2001**, *113*, 4013–4015; *Angew. Chem. Int. Ed.* **2001**, *40*, 3895–3897; d) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3008; e) M. Lautens, W. T. Klute, *Chem. Rev.* **1996**, *96*, 49–92.

[9] a) R. E. Looper, M. T. C. Runnegar, R. M. Williams, *Angew. Chem.* **2005**, *117*, 3947–3949; *Angew. Chem. Int. Ed.* **2005**, *44*, 3879–3881; b) J. Kobayashi, F. Kanda, M. Ishibashi, H. Shigemori, *J. Org. Chem.* **1991**, *56*, 4574–4576; c) G. S. Skinner, P. R. Wunz, *J. Am. Chem. Soc.* **1951**, *73*, 3814–3815.

[10] a) T. Endo, M. Tsuda, J. Fromont, J. Kobayashi, *J. Nat. Prod.* **2007**, *70*, 423–424; b) E. V. Costa, M. L. B. Pinheiro, C. M. Xavier, J. R. A. Silva, A. C. F. Amaral, A. D. L. Souza, A. Barison, F. R. Campos, A. G. Ferreira, G. M. C. Machado, L. L. P. Leon, *J. Nat. Prod.* **2006**, *69*, 292–294; c) Y. L. Lin, R. L. Huang, C. M. Chang, Y. H. Kuo, *J. Nat. Prod.* **1997**, *60*, 982–985.

[11] a) W. S. Messer, Y. F. Abuh, Y. Liu, S. Periyasamy, D. O. Ngur, M. A. N. Edgar, A. A. Eissadi, S. Sbeih, P. G. Dunbar, S. Roknich, T. Rho, Z. Fang, B. Ojo, H. Zhang, J. J. Huzl, P. I. Nagy, *J. Med. Chem.* **1997**, *40*, 1230–1246; b) P. G. Dunbar, G. J. Durant, T. Rho, B. Ojo, J. J. Huzl, D. A. Smith, A. A. El-Assadi, S. Sbeih, D. O. Ngur, S. Periyassamy, W. Hoss, W. S. Messer, Jr., *J. Med. Chem.* **1994**, *37*, 2774–2782; c) P. G. Dunbar, G. J. Durant, Z. Fang, Y. F. Abuh, A. A. El-Assadi, D. O. Ngur, S. Periyasamy, W. P. Hoss, W. S. Messer, *J. Med. Chem.* **1993**, *36*, 842–847.

[12] G. Malin, R. Iakobashvili, A. Lapidot, *J. Biol. Chem.* **1999**, *274*, 6920–6929.

[13] a) V. Nair, G. Chi, R. Ptak, N. Neamati, *J. Med. Chem.* **2006**, *49*, 445–447; b) S. Zhou, E. R. Kern, E. Gullen, Y. C. Cheng, J. C. Drach, S. Matsumi, H. Mitsuya, J. Zemlicka, *J. Med. Chem.* **2004**, *47*, 6964–6972.

[14] K. Chantrapromma, S. James, M. Manis, B. Ganem, *Tetrahedron Lett.* **1980**, *21*, 2475–2476.

[15] B. Rodrýguez, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2888–2891.

[16] R. Pattarini, R. J. Smeyne, J. I. Morgan, *Neuroscience* **2007**, *145*, 654–668.

[17] a) R. Chinchilla, C. Najera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667–2722; b) A. Turck, N. Ple, F. Mongin, G. Queguiner, *Tetrahedron* **2001**, *57*, 4489–4505.

[18] a) M. Mayr, M. R. Buchmeiser, *Macomol. Rapid Commun.* **2004**, *25*, 231–236; b) M. Mayr, K. Wurst, K. H. Ongania, M. R. Buchmeiser, *Chem. Eur. J.* **2004**, *10*, 1256–1266; **2004**, *10*, 2615–2622.

[19] a) H. Finch, E. A. Peterson, S. A. Ballard, *J. Am. Chem. Soc.* **1952**, *74*, 2016–2018; b) R. F. Evans, A. V. Robertson, *Aust. J. Chem.* **1973**, *26*, 1599–1605; c) A. R. Katrizky, S. K. Singh, H. Y. He, *J. Org. Chem.* **2002**, *67*, 3115–3117.

[20] K. Chantrapromma, B. Ganem, *Tetrahedron Lett.* **1981**, *22*, 23–24.

[21] M. Zhang, H. F. Jiang, H. L. Liu, Q. H. Zhu, *Org. Lett.* **2007**, *9*, 4111–4113.

[22] a) S. Tobisch, *Chem. Eur. J.* **2007**, *13*, 9127–9136; b) A. Motta, G. Lanza, I. L. Fragala, T. J. Marks, *Organometallics* **2004**, *23*, 4097–4104; c) S. Tobisch, *J. Am. Chem. Soc.* **2005**, *127*, 11979–11988; d) A. Motta, I. L. Fragala, T. J. Marks, *Organometallics* **2006**, *25*, 5533–5539; e) G. Huerta, L. Fomina, *THEOCHEM* **2006**, *761*, 107–112.

[23] a) M. Zhang, H. F. Jiang, A. Z. Wang, *Synlett* **2007**, *20*, 3214–3218; b) M. Zhang, H. F. Jiang, *Eur. J. Org. Chem.* **2008**, 3519–3523.

[24] D. R. Coulson, *Tetrahedron Lett.* **1971**, *12*, 429–430.

[25] A. L. Casalnuovo, J. C. Calabrese, D. Milstein, *J. Am. Chem. Soc.* **1988**, *110*, 6738–6744.

[26] Y. Uchimaru, *Chem. Commun.* **1999**, *12*, 1133–1134.

[27] M. Tokunaga, M. Eckert, Y. Wakatsuki, *Angew. Chem.* **1999**, *111*, 3416–3419; *Angew. Chem. Int. Ed.* **1999**, *38*, 3222–3225.

[28] a) C. G. Hartung, A. Tillack, H. Trauthwein, M. Beller, *J. Org. Chem.* **2001**, *66*, 6339–6343; b) M. Kawatsura, J. F. Hartwig, *Organometallics* **2001**, *20*, 1960–1964; c) M. Beller, C. Breindl, M. Eichberger, C. G. Hartung, J. Seayad, O. R. Thiel, A. Tillack, H. Trauthwein, *Synlett* **2002**, *10*, 1579–1594.

[29] J. W. Sun, S. A. Kozmin, *Angew. Chem.* **2006**, *118*, 5113–5115; *Angew. Chem. Int. Ed.* **2006**, *45*, 4991–4993.

[30] Y. M. Wu, Y. Li, J. Deng, *Tetrahedron Lett.* **2005**, *46*, 5357–5360.

[31] Gaussian 03, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A., Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari,

J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford, CT, **2004**.

[32] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, 37, 785–789.

Received: July 21, 2008
Revised: August 22, 2008
Published online: November 14, 2008