ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Catalytic intermolecular β-C–H alkenylation of α-enamino-ketones with simple alkynes†

Cite this: *Chem. Commun.*, 2014, **50**, 5230

Received 2nd October 2013,
Accepted 4th November 2013

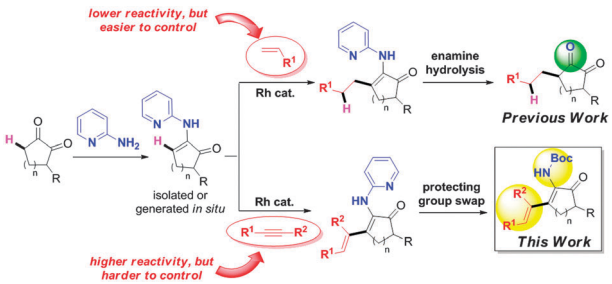
DOI: 10.1039/c3cc47556e

www.rsc.org/chemcomm

Zhiqian Wang,‡[ab] Brandon J. Reinus‡[a] and Guangbin Dong*[a]

A unique strategy to synthesize β-alkenylated α-enamino-ketones *via* catalytic C–H/alkyne coupling is described. The slow addition of alkyne substrates and the use of NaI as an additive play key roles in controlling the alkyne insertion. Replacement of the pyridyl group with carbamates was also developed. This method allows for rapid synthesis of highly functionalized vinyl-substituted enamino-ketones.

The functional group-directed addition of aromatic C–H bonds across alkynes, pioneered by Murai,[1] provided a site-selective and atom-economical[2] method for preparing alkenyl substituted compounds.[3] This process generally involves oxidative addition of transition metals into aryl C–H bonds, followed by migratory insertion of the resulting metal hydrides into alkynes and subsequent reductive elimination to provide the alkenylation products.[4] In contrast, the related addition of vinyl C–H bonds across alkynes is more challenging, likely due to the more sensitive nature of olefins, thus remaining underdeveloped. Coupling of alkynes with acrylates/acylamides was first reported by Mitsudo–Watanabe,[5] and improvements were recently achieved by Nishimura–Uemura[6] and Plietker,[7] all employing Ru complexes as the catalysts.[8] These seminal efforts suggest that the vinyl C–H/alkyne couplings could be a highly attractive method for preparing 1,3-diene compounds; however, the scope of the vinyl compounds that can undergo this transformation so far has been mainly limited to linear esters and amides using carbonyl as the directing group.[9] Recently, we discovered that the vinyl C–H bonds of 2-aminopyridine-derived enamino-ketones can be efficiently activated and coupled with a variety of terminal olefins.[10] In this communication, we describe our development of an intermolecular Rh-catalyzed enamine-directed vinyl C–H/alkyne coupling to prepare olefin-substituted cyclic α-enamino-ketones, and also demonstrate that, instead of enamine hydrolysis, the 2-aminopyridyl group can be effectively converted to the more synthetically useful carbamates (Scheme 1).



Scheme 1 Enamine-directed vinyl C–H/olefin and alkyne couplings.

Enamino-ketones are a class of organic compounds often employed as key intermediates or building blocks for the synthesis of nitrogen-containing molecules.[11] In addition, this structural motif has also been found in a number of biological active molecules and food chemicals.[12,13] Direct alkenylation of α-enamino-ketones *via* C–H functionalization would provide an efficient approach to access highly functionalized 2-amino-2,4-diene-1-one compounds, which permits further derivatizations; however, this transformation remains elusive.[14] Only recently Glorius reported an elegant C–H oxidative Heck-type reaction to achieve vinylation of α-enamide-esters, albeit requiring over two equivalents of copper salts as an oxidant.[15] Hence, direct addition of vinyl C–H bonds across alkynes would provide a complementary and redox-neutral approach to generate the desired alkenylated enaminoketones. Based on our previous efforts towards C–H/olefin coupling,[10] 2-aminopyridine-derived cyclic enamino-ketones are expected to be suitable substrates to couple with simple alkynes (Scheme 1). However, the challenge is two-fold: (1) compared to olefin insertion, the insertion of alkynes is more difficult to control due to the high affinity and reactivity of alkynes with transition metals, which often leads to self-dimerization[16] and/or multiple insertions;[17] (2) it is nontrivial to remove the robust pyridyl group in the presence of many reactive functional groups, such as ketones, enamines and 1,3-dienes.

To address these challenges, our initial study employed cyclic enamino-ketone **1a** as the model substrate and phenylacetylene as

[a] *Department of Chemistry, University of Texas at Austin, Austin, TX 78712, USA*
[b] *Department of Organic Chemistry, Beijing University of Chemical Technology, 100029 Beijing, People's Republic of China*

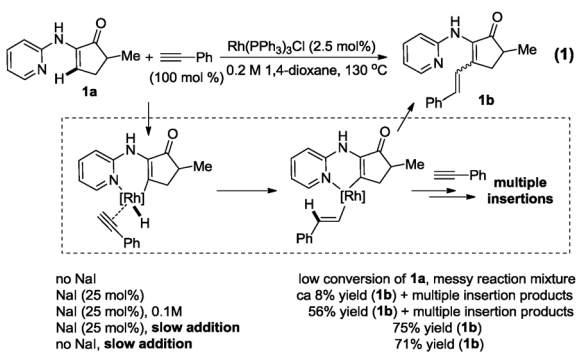
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data. CCDC 966192–966194. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47556e

‡ Z.W. and B.J.R. contributed equally.

the alkyne coupling partner (eqn (1)). As expected, the optimal conditions discovered for olefin insertion ($Rh(PPh_3)_3Cl$ or $[Rh(coe)_2Cl]_2$ in dioxane) only resulted in low conversion of **1a** and complicated reaction mixtures caused by side reactions of phenylacetylene. A number of monodentate and bidentate phosphine ligands were examined, but none was found to enhance the reactivity and selectivity. Halide additives were previously reported to be effective for acrylate–alkyne coupling reactions.[6] Indeed, the use of 1 equiv. of NaI significantly promotes the conversion of enamino-ketone **1a**, likely due to its role of inhibiting metal vinylidene formation; however, the major products were found to have multiple alkyne insertions (confirmed by LC-MS). To solve this problem, we hypothesized that given the high binding affinity of alkynes with Rh if we could keep the alkyne substrate in a low concentration, the mono-insertion product would be favoured. Indeed, when we diluted the reaction mixture and slowly added phenylacetylene through a syringe-pump, the desired mono-alkyne-insertion product **1b** was isolated in a 75% yield (Scheme 2). The factor of concentration was found to be more crucial, as in the absence of NaI; **1b** was still isolated in a 71% yield.

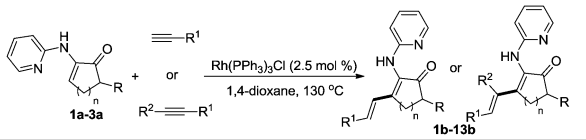
With the optimized conditions in hand, the scope of cyclic enamino-ketones and alkynes was explored (Table 1). A variety of terminal alkynes reacted and gave good to excellent yields (entries 1–6). The alkenylation proceeded with complete regioselectivity, and only anti-Markovnikov addition products were observed. It is interesting to note that both aryl and alkyl-substituted, as well as sterically hindered and less hindered alkynes reacted smoothly. In addition, internal alkynes were also found to be suitable substrates (entries 8–10). Due to the decreased reactivity and lower binding affinity of internal alkynes, slow addition of these substrates was not necessary. For a similar reason, reactions with bulky alkyne substrates, such as 3,3-dimethylbutyne, also proceed well without slow addition (entries 2–4). Furthermore, the six-membered α-enamino-ketones underwent the C–H/alkyne coupling to provide the desired alkenylation products (entries 11–14). Notably, sterically hindered terminal alkynes gave excellent selectivity for the *E*-alkene products; however, a significant amount of *Z*-alkene products were formed with disubstituted alkynes. It is therefore likely that, for the disubstituted-alkyne insertions, the initially formed *E*-alkene products (kinetic product) slowly isomerise to the more thermodynamically stable *Z* products.[18]

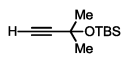
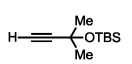
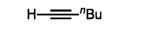
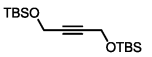
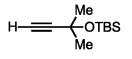
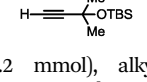
Given that the α-enamino-ketones were prepared *via* condensation between 2-aminopyridine and 1,2-diketones,[10] a tandem three-component coupling was explored next (Table 2). Not surprisingly,



Scheme 2 Coupling between **1a** and phenylacetylene.

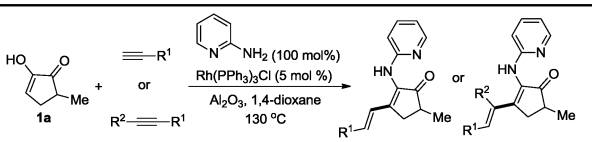
Table 1 Alkenylation of cyclic enamino-ketones with simple alkynes[a]



Entry	Enamino-ketone	Alkyne	Yield ($E:Z$)[b]
1	n = 1, R = Me	H—≡—Ph	**1b**, 75[c,d] (3.5 : 1)
2	n = 1, R = Me	H—≡—^{t}Bu	**2b**, 99 (>20 : 1)
3	n = 1, R = Me		**3b**, 99[c] (>20 : 1)
4	n = 1, R = Me		**3b**, 78 (>20 : 1)
5	n = 1, R = Me	H—≡—TMS	**4b**, 76[c,d] (>20 : 1)
6	n = 1, R = Me	H—≡—^{n}Bu	**5b**, 94[b,c] (5.6 : 1)
7	n = 1, R = Me		**6b**, 74[b,c] (5.6 : 1)
8	n = 1, R = Me	Ph—≡—Ph	**7b**, 99[c] (2.0 : 1)
9	n = 1, R = Me	Et—≡—Et	**8b**, 67[c] (2.5 : 1)
10	n = 1, R = Me		**9b**, 60[c] (1.3 : 1)
11	n = 2, R = Me	H—≡—^{t}Bu	**10b**, 99 (>20 : 1)
12	n = 2, R = Me		**11b**, 92[c] (>20 : 1)
13	n = 2, R = H	H—≡—^{t}Bu	**12b**, 87 (>20 : 1)
14	n = 2, R = H		**13b**, 92[c] (>20 : 1)

[a] Conditions: enaminoketone (0.2 mmol), alkyne (0.2–0.4 mmol), $Rh(PPh_3)_3Cl$ (2.5 mol%), 1,4-dioxane, 130 °C, 20 h. [b] Isolated yields. *E*/*Z* ratio was determined by ^{1}H-NMR. [c] NaI (25 mol%) was used. [d] Alkyne was diluted with 1,4-dioxane and added slowly in 8 h *via* a syringe pump.

Table 2 Three-component coupling to give β-alkenyl-α-enamino-ketones[a]

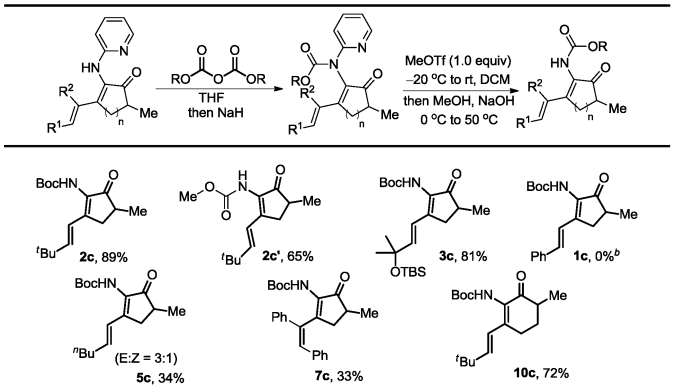


Entry	Alkyne	Yield[b] ($E:Z$)
1	H—≡—Ph	**1b**, trace[c,d]
2	H—≡—^{t}Bu	**2b**, 41% (>20 : 1)
3	H—≡—^{t}Bu	**2b**, trace[d,e]
4	Ph—≡—Ph	**7b**, 64% (1 : 2.5)
5	Ph—≡—Ph	**7b**, 76% (1 : 3.6)[d]
6	Et—≡—Et	**8b**, 51% (1 : 2.5)

[a] Conditions: **1a** (0.2 mmol), 2-aminopyridine (0.2 mmol), alkyne (0.4 mmol), $Rh(PPh_3)_3Cl$ (5 mol%), 1,4-dioxane, 130 °C, 20 h. [b] Isolated yields. *E*/*Z* ratio was determined by ^{1}H-NMR. [c] Alkyne was diluted with 1,4-dioxane and added slowly in 8 h *via* a syringe pump. [d] NaI (25 mol%) was used. [e] The reaction stopped after the condensation of the diketone and 2-aminopyridine.

the use of phenylacetylene only gave a very low conversion (entry 1), because the enamine formation prefers high reaction

Table 3 Replacement of the pyridyl group with carbamates[a]

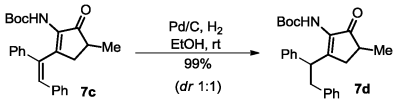


[a] Isolated yields over two steps. [b] The first step provided a 45% yield of the Boc protection product; however, no de-pyridyl product was found during the second step.

concentration whereas the C–H coupling with phenylacetylene requires a low concentration (*vide supra*). However, the sterically hindered terminal alkynes and disubstituted alkynes proceeded well in the three-component couplings. It is interesting to note that the use of NaI with 3,3-dimethylbutyne significantly inhibited the reaction, yielding only a trace amount of products; however, in the absence of NaI, the desired adduct was isolated in a 41% yield (entries 2 and 3). In contrast, for the diphenylacetylene insertion, a slightly increased yield with adding NaI was observed (entries 4 and 5). The exact role of NaI in these reactions will be explored systematically in the future. Under these reaction conditions, the thermodynamic products (*Z* alkene) were isolated as the major isomer (entries 4–5).

We next explored the feasibility to replace the pyridyl group with the more user-friendly carbamates. Although there are several examples previously reported for removing pyridyl groups from amines,[19] to the best of our knowledge, none involves substrates with rich functional groups, such as enamines, ketones, and 1,3-dienes. Stimulated by this chemoselective challenge, we examined a number of reaction conditions, and ultimately a two-pot (three-step) procedure was found to be most effective (Table 3). Under these modified conditions, the amine (in the aminopyridine) was first protected by dicarbonates, followed by methylation of the pyridine nitrogen and then methanolysis under basic conditions, providing the desired carbamates. One key step is to control the equivalents of the methylating agents; for example, the use of excess methyl triflate led to significantly lower yields of the desired product (or even no product). Note that the more sterically hindered substrates provided much higher yields in the pyridyl-carbamate swap reaction than the less hindered ones (no product except decomposition was observed for the phenyl substituted substrate);[20] however, the exact reaction is still unclear.

Finally, our preliminary study indicated that the alkenyl substituent can be chemoselectively reduced in an excellent yield *via* catalytic hydrogenation (eqn (2)). Given that the previous alkene insertion with α-enamino-ketones was limited to terminal olefins that only gives linear substitutions,[10] this C–H/alkyne coupling method provides a complementary approach to access the branched products.



(2)

We thank UT Austin, CPRIT, the Welch Foundation (F-1781), the Frasch Foundation and NSF career award (CHE-1254935). G. D. is a Searle Scholar. Dr Lynch is acknowledged for the X-ray crystallography work. We thank Johnson Matthey for donation of Rh.

Notes and references

1 F. Kakiuchi, Y. Yamamoto, N. Chatani and S. Murai, *Chem. Lett.*, 1995, 681.
2 B. Trost, *Science*, 1991, **254**, 1471.
3 For leading Reviews: (*a*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (*b*) F. Kakiuchi and S. Murai, *Acc. Chem. Res.*, 2002, **35**, 826; (*c*) D. Colby, R. Bergman and J. Ellman, *Chem. Rev.*, 2012, **110**, 624; (*d*) C.-H. Jun, C. W. Moon and D.-Y. Lee, *Chem.–Eur. J.*, 2002, **8**, 2422.
4 A unique dinuclear Pd complex-catalysed arene-alkyne coupling reaction is reported: N. Tsukada, T. Mitsuboshi, H. Setoguchi and Y. Inoue, *J. Am. Chem. Soc.*, 2003, **125**, 12102.
5 T. Mitsudo, S. Zhang, M. Nagao and Y. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1991, 598.
6 T. Nishimura, Y. Washitake and S. Uemura, *Adv. Synth. Catal.*, 2007, **349**, 2563.
7 (*a*) N. Matthias Neisius and B. Plietker, *Angew. Chem., Int. Ed.*, 2009, **48**, 5752; (*b*) T. Schabel and B. Plietker, *Chem.–Eur. J.*, 2013, **19**, 6938.
8 For a report of using solid-support Ru catalysts, see: H. Miura, S. Shimura, S. Hosokawa, S. Yamazoe, K. Wada and M. Inoue, *Adv. Synth. Catal.*, 2011, **353**, 2837.
9 Only a single ketone substrate was reported previously (ref. 7*a*).
10 Z. Wang, B. Reinus and G. Dong, *J. Am. Chem. Soc.*, 2012, **134**, 13954.
11 For a recent review on enamino-ketones see: (*a*) G. Negri, C. Kascheres and A. Kascheres, *J. Heterocycl. Chem.*, 2004, **41**, 461; for recent synthetic applications, see: (*b*) A. Dounay, L. Overman and A. Wrobleski, *J. Am. Chem. Soc.*, 2005, **127**, 10186; (*c*) R. Figueroa, R. Froese, Y. He, J. Kosin and C. Theriault, *Organometallics*, 2011, **30**, 1695; (*d*) S. D. Kuduk, *et al.*, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2538; (*e*) J. Cossy, C. Poitevin, L. Salle and D. Pardo, *Tetrahedron Lett.*, 1996, **37**, 6709; (*f*) T. Taniguchi, G. Tanabe, O. Muraoka and H. Ishibashi, *Org. Lett.*, 2008, **10**, 197.
12 (*a*) A. Martelli, *et al.*, *J. Med. Chem.*, 2013, **56**, 4718; (*b*) V. Cecchetti, *et al.*, *J. Med. Chem.*, 2003, **46**, 3670; (*c*) C. Emanuele, *et al.*, *Bioorg. Med. Chem.*, 2005, **13**, 5581.
13 R. Tressl, B. Helak, H. Koppler and D. Rewicki, *J. Agric. Food Chem.*, 1985, **33**, 1132.
14 For examples of the alkenylation of β-enamino-ketones, see: (*a*) Y. Chun, Y. Ko, H. Shin and S. Lee, *Org. Lett.*, 2009, **11**, 3414; (*b*) T. Fujimoto, K. Endo, H. Tsuji, M. Nakamura and E. Nakamura, *J. Am. Chem. Soc.*, 2008, **130**, 4492; (*c*) Y. Yu, M. Niphakis and G. Georg, *Org. Lett.*, 2011, **13**, 5932.
15 (*a*) T. Besset, N. Kuhl, F. W. Patureau and F. Glorius, *Chem.–Eur. J.*, 2011, **17**, 7167; (*b*) J. Du, B. Zhou, Y. Yang and Y. Li, *Chem.–Asian J.*, 2013, **8**, 1386.
16 (*a*) B. Claudio and P. Maurizio, *Chemtracts: Inorg. Chem.*, 1993, **5**, 225; (*b*) M. Puerta and P. Valerga, *Coord. Chem. Rev.*, 1999, 977.
17 (*a*) H. Horie, I. Koyama, T. Kurahashi and S. Matsubara, *Chem. Commun.*, 2011, **47**, 2658; (*b*) J.-R. Kong and M. J. Krische, *J. Am. Chem. Soc.*, 2006, **128**, 16040.
18 After sitting at room temperature for one week, compound **7b** fully isomerised to its Z isomer.
19 (*a*) N. Dastbaravardeh, M. Schmürch and M. D. Mihovilovic, *Org. Lett.*, 2012, **14**, 1930; (*b*) S. Pan, K. Endo and T. Shibata, *Org. Lett.*, 2011, **13**, 4692; (*c*) V. Smout, *et al.*, *J. Org. Chem.*, 2013, **78**, 9803; (*d*) K. J. Jana, S. Grimme and A. Studer, *Chem.–Eur. J.*, 2009, **15**, 9078.
20 Replacement of methanolysis with $NaBH_4$ reduction was attempted but did not improve the yields for the low yielding substrates.

