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Palladium-Catalysed Cyclisation of *N*-Alkynyl Aminomalonates

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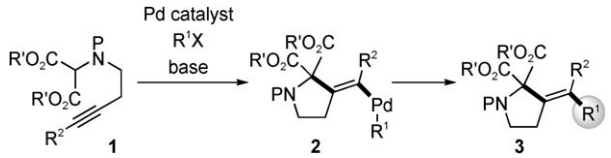
Pyrrolidines and pyrrolidinones are highly important structural motifs in organic chemistry. They are present in many ligands for asymmetric catalysis, as catalysts in the ever-growing field of organocatalysis,[1] and in a vast number of natural products.[2] Moreover, pyrrolidines and nitrogen heterocycles, in general, are exceedingly important motifs in medicinal chemistry. The pursuit of new and efficient methods for the synthesis of pyrrolidines and pyrrolidinones, therefore remains an important goal in modern organic synthesis. We envisaged a novel approach to pyrrolidines by palladium-catalysed intramolecular cyclisation of aminomalonates onto alkynes, which would result in the formation of two C–C bonds and a stereodefined alkene in a single step (**1**→**2**→**3**, Scheme 1);[3] an analogous scheme has been employed successfully for the cyclisation of 4-alkynyl malonates and related compounds,[4–6] and a related three-component reaction for the synthesis of 3-alkylidene pyrrolidines has been developed by Balme and co-workers.[7] Apart from the beautiful indium-catalysed Conia-ene reaction for the formation of pyrrolidines and pyrrolidinones reported from Hatakeyama's group,[8] the cyclisation of α-aminomalonates onto alkynes has barely been studied.[9]



Scheme 1. Proposed Pd-catalysed cyclisation. (R^1 = aryl, vinyl, alkynyl, allyl).

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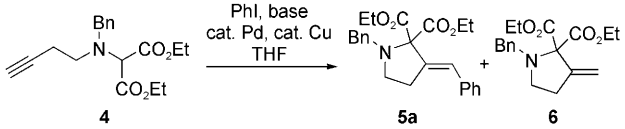
Our initial efforts focussed on the cyclisation of *N*-benzyl-protected aminomalonate **4**[10] to form **5a**[11] under palladium and copper catalysis[4c,h] (Table 1). Thus, exposure of **4** to 5.0 mol% [$PdCl_2$(dppf)] (dppf = 1,1′-bis(diphenylphosphino)ferrocene), 10.0 mol% CuI and stoichiometric *t*BuOK in THF at 60 °C delivered the desired pyrrolidine **5a** in 18% yield, along with a fully substituted alkene by-product product **13g** (Table 1, entry 1). Reducing the catalyst loading to

Table 1. Initial screen of conditions.[12]



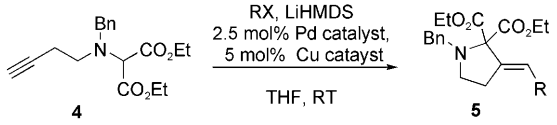
Entry[a]	Pd source[l]	PhI [equiv]	Base [equiv]	*t* [h]	Yield **5a** [%][c]	Yield **6** [%]
1[b,c]	[$PdCl_2$(dppf)]	1.0	2.0	15	18	–
2	[$PdCl_2$(dppf)]	1.0	1.0	0.25	59	20
3	[$PdCl_2$(dppf)]	2.0	1.5	0.25	58	–
4	[$PdCl_2$(dppf)]	–	1.5	15	–	(48[d])
5[e]	[$Pd(Ph_3P)_4$]	1.5	1.0	0.5	16	29
6[f]	[$PdCl_2$(dppe)]	1.5	1.0	0.25	16	15
7[g,h]	[$PdCl_2$(xantphos)]	1.5	1.0	0.5	45	8
8[h]	[$PdCl_2$(dppf)]	1.5	1.0	0.25	71	–
9[h,i]	[$PdCl_2$(dppf)]	1.5	1.0	0.25	72	–
10[h,j]	[$PdCl_2$(dppf)]	1.5	1.0	0.25	76	–
11[h,k]	[$PdCl_2$(dppf)]	1.5	1.0	20	–	–

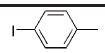
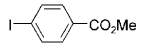
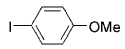
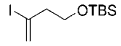
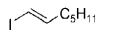
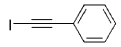
[a] Reaction conditions: **4** (1.0 equiv), PhI (1.0–2.0 equiv), [$PdCl_2$(dppf)] (2.5 mol%), CuI (5.0 mol%), *t*BuOK (1.0–2.0 equiv), in THF at ambient temperature. [b] Reaction conducted at 60 °C. [c] [$PdCl_2$(dppf)] (5.0 mol%) and CuI (10.0 mol%) were used; the product **13g** was also isolated (25%). [d] The product resulting from ethoxydecarbonylation and alkene isomerisation of **6** was the only isolated compound.[6b] [e] The Sonogashira product was also isolated (32%). [f] Products resulting from ethoxydecarbonylation and alkene isomerisation of **6** were also observed.[6b] [g] [$PdCl_2$(xantphos)] (5.0 mol%) was used and recovered starting material was isolated (33%). [h] The malonate was deprotonated separately prior to addition to the reaction mixture. [i] NaH was used as the base. [j] Lithium bis(trimethylsilyl)amide was used as the base. [k] *N,O*-Bis(trimethylsilyl)acetamide was used; no conversion was detected by TLC analysis after 4 h whereas after 20 h the Glaser coupling product was isolated (22%). [l] dppf = 1,1′-bis(diphenylphosphino)ferrocene; dppe = 1,2-bis(diphenylphosphino)ethane; xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

2.5 mol% Pd and 5.0 mol% Cu with a concomitant reduction of the reaction temperature to ambient increased the yield of **5a** to 59% with the methylene pyrrolidine **6** being isolated in 20% yield (Table 1, entry 2). Increasing the equivalents of iodobenzene or changing the ligands on palladium proved to be detrimental. Adding the deprotonated malonate to a solution of the catalysts and iodobenzene in THF resulted in the formation of **5a** in much improved yields with concomitant reduction in the amount of by-products formed (Table 1 entries 7–10). Strong lithium, sodium and potassium bases were equally effective in the reaction (Table 1 entries 8–10); however, the use of *N*,*O*-bis(trimethylsilyl)acetamide[4d] proved ineffective.

With the optimised reaction conditions in hand the scope of the halide coupling partner was investigated (Table 2). Electron-deficient as well as electron-rich aryl iodides (Table 2, entries 1–4) participate in the reaction with the corresponding pyrrolidines **5b–e** being isolated in 68–73% yield. As expected, an aryl iodide could be selectively coupled in the presence of an aryl bromide (Table 2, entry 5). Vinyl iodides (Table 2, entries 6 and 7) and iodo alkynes[4c] (Table 2, entry 8) are also competent coupling partners giving the desired pyrrolidines in 54–56% yield. The cross-coupling with allyl bromide[4c,d] was also efficient with no allylation at the malonate carbon being detected (Table 2, entry 9). However, aryl and vinyl bromides, and allyl acetate were poor substrates for the reaction (Table 2, entries 10–12).

Table 2. Variation of halide coupling partner.[12]

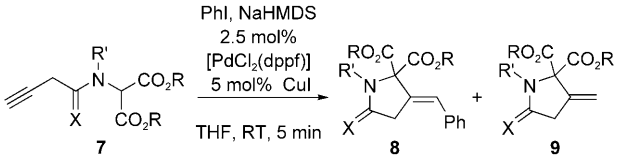


Entry[a]	RX[f]	*t* [min]	Product	Yield [%]
1		5	**5b**	73
2		5	**5c**	68
3		5	**5d**	70
4[b]		5	**5e**	69
5		5	**5f**	64
6		5	**5g**	55
7[c]		5	**5h**	54
8[c]		5	**5i**	56
9		5	**5j**	73
10		1200	**5k**	20
11[d]		1200	**5a**	–
12[e]		30	**5j**	15

[a] Reaction conditions: **4** (1.0 equiv), RX (1.5 equiv), [$PdCl_2$(dppf)] (2.5 mol%), CuI (5.0 mol%), LiHMDS (1.0 equiv, 1 M in toluene), in THF at ambient temperature. [b] Product is contaminated with **6** (approximately 7%); yield adjusted for purity. [c] NaHMDS used in place of LiHMDS. [d] No conversion was observed. [e] The reaction was quenched after 30 min and **6** was also isolated (51%). [f] Bn = benzyl.

Variation within the malonate ester groups and the protecting group on nitrogen was investigated next (Table 3). A common side-product was the corresponding *exo*-methylene

Table 3. Variation of malonate and nitrogen protecting group.[12]



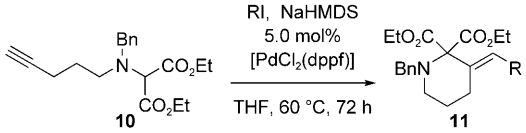
Entry[a]	substrate [R′, R, X][c]	Yield **8** [%], (**8**:**9**)
1	**7a**, Bn, *t*Bu, H_2	73 (32:1)
2	**7b**, Me, Et, H_2	66 (9:1)
3	**7c**, PMB, *t*Bu, H_2	58 (3:1)
4	**7d**, CO_2Me, Et, H_2	72 (10:1)
5	**7e**, CO_2Bn, Et, H_2	72 (11:1)
6	**7f**, CO_2Bn, *t*Bu, H_2	42 (3.2:1)
7[b]	**7g**, H, Et, O	–

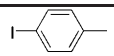
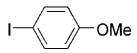
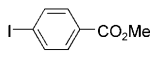
[a] Reaction conditions: **7** (1.0 equiv), PhI (1.5 equiv), [$PdCl_2$(dppf)] (2.5 mol%), CuI (5.0 mol%), NaHMDS (1.0 equiv, 0.6 M in toluene), in THF for 5 min at ambient temperature. [b] Reaction quenched after 25 min. [c] PMB = 4-methoxybenzyl.

pyrrolidine **9**.[13] The formation of this side-product could be reduced by employing NaHMDS in place of LiHMDS (HMDS = hexamethyldisilazide). The diethyl and di-*tert*-butyl malonates **7a–c** cyclised without incident (Table 3, entries 1–3). Moreover, various substituents on the nitrogen, including benzyl (entry 1), methyl (entry 2), 4-methoxybenzyl (entry 3) and benzyl- and methyloxycarbonyl (entries 4–6) are all tolerated in the reaction. Attempted cyclisation of the corresponding amido malonate **7g** (Table 3, entry 7) resulted in rapid decomposition of the substrate.

Slight modification of the experimental procedure allowed for the synthesis of piperidines (Table 4).[14] Again, both electron-rich and electron-deficient aryl iodides were competent coupling partners.

Table 4. Synthesis of piperidines.[12]

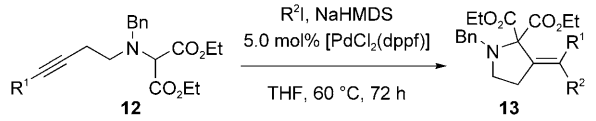


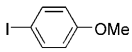
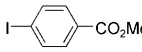
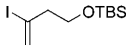
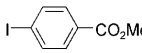
Entry[a]	RI	Product	Yield [%]
1		**11a**	70
2		**11b**	42
3		**11c**	56

[a] Reaction conditions: **10** (1.0 equiv), RI (1.5 equiv), [$PdCl_2$(dppf)] (5.0 mol%), NaHMDS (1.0 equiv, 0.6 M in toluene), in THF for 72 h at 60 °C.

Having demonstrated the synthesis of trisubstituted alkylidene pyrrolidines and piperidines our efforts turned to the synthesis of stereodefined fully substituted alkylidene pyrrolidines.[4b,15] Using the reaction conditions that were successful for the synthesis of the piperidines,[14] the synthesis of a wide range of tetrasubstituted alkenes **13** in 62–88% yield as single diastereomers was achieved (Table 5). As with the previous substrates electronically diverse aryl iodides were well-tolerated coupling partners as were vinyl iodides.

Table 5. Synthesis of fully substituted alkenes.[12]



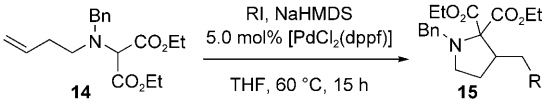
Entry[a]	R^1, substrate	R^2I	Product	Yield [%]
1[b]	Me, **12a**		**13a**	88
2[c]	Me, **12a**		**13b**	82
3	Me, **12a**		**13c**	75
4[d]	Me, **12a**		**13d**	62
5	*n*Bu, **12b**		**13e**	68
6	*n*Bu, **12b**		**13f**	68
7[e]	Ph, **12c**		**13g**	83

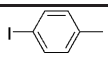
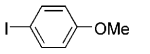
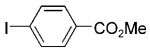
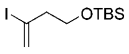
[a] Reaction conditions: **12** (1.0 equiv), R^2I (1.5 equiv), [$PdCl_2$(dppf)] (5.0 mol%), NaHMDS (1.0 equiv, 0.6 M in toluene), in THF, 72 h, 60 °C. [b] Reaction complete in 3 h at RT. [c] Reaction complete in 15 h. [d] A 1.0:5.6 mixture of starting material:product was isolated, yield is given for the amount of product present. [e] Reaction conducted at 60 °C for 60 h.

Lastly we conducted preliminary experiments into the cyclisation of the corresponding olefinic substrate **14**.[9b,16–20] Under the same conditions as used for the internal alkyne substrates, the alkenyl malonate **14** gave the corresponding pyrrolidines **15** in 33–70% yield (Table 6). As with the alkynyl substrates **4**, aryl iodides were better coupling partners for the reaction (Table 6, entries 1–3) than the corresponding alkenyl iodides (Table 6, entry 4).

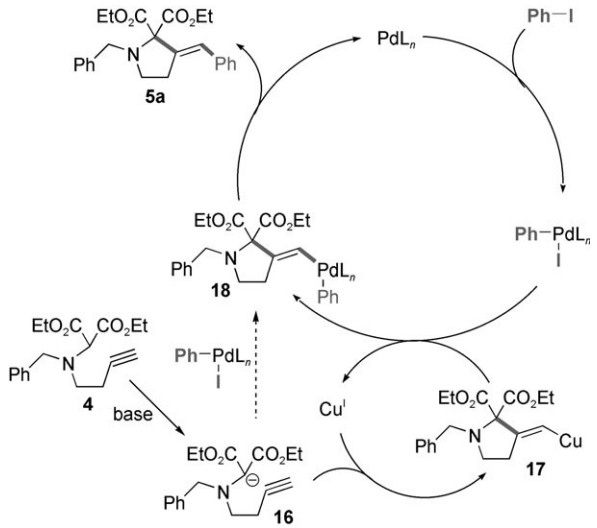
A plausible mechanism for the reaction, analogous to that proposed in the all carbon series is given below (Scheme 2).[19] In the presence of a copper salt the deprotonated malonate **16** undergoes cyclisation to give the vinylcopper species **17**. After oxidative addition of iodobenzene to the Pd^0 catalyst, transmetallation occurs with the vinylcopper species giving **18**, which on reductive elimination delivers the product **5a** and regenerates the Pd^0 catalyst. In the absence of a copper(I) salt, cyclisation of the anion **16** onto the alkyne occurs under Pd^{II} catalysis to give **18** directly (dotted arrow).

Table 6. Use of alkenyl aminomalonates.



Entry[a]	RI	Product	Yield [%]
1[b]		**15a**	67
2		**15b**	66
3		**15c**	70
4		**15d**	33

[a] Reaction conditions: **14** (1.0 equiv), R^2I (1.5 equiv), [$PdCl_2$(dppf)] (5.0 mol%), NaHMDS (1.0 equiv, 0.6 M in toluene), in THF, 60 °C, 15 h. [b] Reaction was conducted at RT for 60 h.



Scheme 2. Proposed cyclisation mechanism.

In summary, we have developed a palladium-catalysed tandem cyclisation/coupling reaction which offers a rapid, mild and efficient route to functionalised pyrrolidines, the products being obtained in moderate to excellent yields as single diastereomers. The reaction tolerates a variety of functional groups including: esters, carbamates, amines, ethers, silyl ethers and aryl bromides; as well as a variety of malonyl esters. Piperidines may also be synthesised using the developed methodology. The described methodology offers a new entry into various pyrrolidine building blocks for use in numerous synthetic applications including natural product synthesis.

Experimental Section

See Supporting Information for full experimental details.

Acknowledgements

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Keywords: aminomalonates · copper · nitrogen heterocycles · palladium · pyrrolidines

[1] For recent reviews of enamine and iminium ion catalysis, see: S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416.

[2] A search of the Beilstein database revealed over 9000 natural products containing a five-membered nitrogen heterocycle.

[3] For a review of the addition of metal enolate derivatives onto unactivated C–C multiple bonds, see: F. Dénès, A. Pérez-Luna, F. Chemla, *Chem. Rev.* **2010**, *110*, 2366.

[4] For related Pd and Pd/Cu-catalysed cyclisations of 4-alkynyl malonates resulting in the formation of two C–C bonds, see: a) G. Fournet, G. Balme, B. Van Hemelryck, J. Goré, *Tetrahedron Lett.* **1990**, *31*, 5147; b) G. Fournet, G. Balme, J. Goré, *Tetrahedron* **1991**, *47*, 6293; c) D. Bouyssi, G. Balme, J. Goré, *Tetrahedron Lett.* **1991**, *32*, 6541; d) I. Coudanne, G. Balme, *Synlett* **1998**, 998; e) G. S. Liu, X. Y. Lu, *Tetrahedron Lett.* **2002**, *43*, 6791; f) D. Bruyère, D. Bouyssi, G. Balme, *Tetrahedron* **2004**, *60*, 4007; g) T. Lomberget, D. Bouyssi, G. Balme, *Synthesis* **2005**, 311; h) N. Coia, D. Bouyssi, G. Balme, *Eur. J. Org. Chem.* **2007**, 3158.

[5] For other related Pd-catalysed cyclisations of malonates and alkynes with the formation of two C–C bonds, see: a) L.-N. Guo, X.-H. Duan, H.-P. Bi, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2006**, *71*, 3325; b) D. H. Zhang, Z. J. Liu, E. K. Yum, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 251.

[6] For related metal-mediated and metal-catalysed cyclisations of 4-alkynyl malonates resulting in the formation of one C–C bond see the following: using Pd, a) N. Monteiro, G. Balme, J. Goré, *Tetrahedron Lett.* **1991**, *32*, 1645; b) N. Monteiro, J. Goré, G. Balme, *Tetrahedron* **1992**, *48*, 10103; c) H. P. Bi, X. Y. Liu, F. R. Gou, L. N. Guo, X. H. Duan, Y. M. Liang, *Org. Lett.* **2007**, *9*, 3527; d) H. P. Bi, X. Y. Liu, F. R. Gou, L. N. Guo, X.-H. Duan, X. Z. Shu, Y. M. Liang, *Angew. Chem.* **2007**, *119*, 7198; *Angew. Chem. Int. Ed.* **2007**, *46*, 7068; e) H. P. Bi, L. N. Guo, F. R. Gou, X. H. Duan, X. Y. Liu, Y. M. Liang, *J. Org. Chem.* **2008**, *73*, 4713; using Ni, f) F. R. Gou, H. P. Bi, L. N. Guo, Z. H. Guan, X. Y. Liu, Y. M. Liang, *J. Org. Chem.* **2008**, *73*, 3837; using Cu, g) D. Bouyssi, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1297; h) U. Jahn, P. Hartmann, I. Dix, P. G. Jones, *Eur. J. Org. Chem.* **2001**, 3333; using Ti or Zn with or without I_2, i) O. Kitagawa, T. Inoue, K. Hirano, T. Taguchi, *J. Org. Chem.* **1993**, *58*, 3106; j) O. Kitagawa, T. Suzuki, T. Inoue, Y. Watanabe, T. Taguchi, *J. Org. Chem.* **1998**, *63*, 9470; k) O. Kitagawa, T. Suzuki, T. Inoue, T. Taguchi, *Tetrahedron Lett.* **1998**, *39*, 7357; l) C. L. Deng, R. J. Song, Y. L. Liu, J. H. Li, *Adv. Synth. Catal.* **2009**, *351*, 3096; using Fe, m) reference [6h]; using only Li, Na or K bases, n) G. Eglinton, M. C. Whiting, *J. Chem. Soc.* **1953**, 3052; o) O. Kitagawa, T. Suzuki, H. Fujiwara, M. Fujita, T. Taguchi, *Tetrahedron Lett.* **1999**, *40*, 4585; using Sc, p) K. Gao, J. Wu, *Org. Lett.* **2008**, *10*, 2251; using positive iodine, q) H. P. Bi, L.-N. Guo, X. H. Duan, F. R. Gou, S. H. Huang, X. Y. Liu, Y. M. Liang, *Org. Lett.* **2007**, *9*, 397.

[7] a) S. Azoulay, N. Monteiro, G. Balme, *Tetrahedron Lett.* **2002**, *43*, 9311; b) B. Clique, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1301.

[8] K. Takahashi, M. Midori, K. Kawano, J. Ishihara, S. Hatakeyama, *Angew. Chem.* **2008**, *120*, 6340; *Angew. Chem. Int. Ed.* **2008**, *47*, 6244.

[9] For related metal-catalysed and metal-mediated reactions for the synthesis of 3-alkyl or 3-alkylidene pyrrolidines, see: a) G. Liu, X. Lu, *Tetrahedron Lett.* **2003**, *44*, 467; b) L. Martinon, S. Azoulay, N. Monteiro, E. P. Kündig, G. Balme, *J. Organomet. Chem.* **2004**, *689*, 3831; c) S. Morikawa, S. Yamazaki, Y. Furusaki, N. Amano, K. Zenke, K. Kakiuchi, *J. Org. Chem.* **2006**, *71*, 3540; d) E. O. Onyango, J. Tsurumoto, N. Imai, K. Takahashi, J. Ishihara, S. Hatakeyama, *Angew. Chem.* **2007**, *119*, 6823; *Angew. Chem. Int. Ed.* **2007**, *46*, 6703.

[10] The aminomalonates were readily prepared according to the method of Chai, see: C. L. L. Chai, J. A. Elix, P. B. Huleatt, *Tetrahedron* **2005**, *61*, 8722.

[11] For the cyclisation of a malonate anion onto a vinylpalladium species for the formation of an alkylidene pyrrolidinone, see reference [9d].

[12] The *E* configuration of the newly installed double bonds in compounds **5a**, **5h**, **5i**, **11c**, **13c**, **13d** and **13e** were assigned by using ^{1}H NMR NOE experiments. The *E* configuration of the remaining products was assigned by analogy.

[13] The *exo*-methylene pyrrolidines can generally be removed by flash chromatography.

[14] The base was added to a mixture of the substrates and the palladium catalyst in THF. No copper catalyst was used.

[15] For the synthesis of fully substituted alkylidene cyclopentanes by the cyclisation of substituted 4-pentynyl malonates by using Mn, see: K. Okuro, H. Alper, *J. Org. Chem.* **1996**, *61*, 5312.

[16] G. Fournet, G. Balme, J. Goré, *Tetrahedron Lett.* **1989**, *30*, 69.

[17] G. Fournet, G. Balme, J. Goré, *Tetrahedron* **1990**, *46*, 7763.

[18] M. Cavicchioli, E. Sixdenier, A. Derrey, D. Bouyssi, G. Balme, *Tetrahedron Lett.* **1997**, *38*, 1763.

[19] D. Bouyssi, G. Balme, G. Fournet, N. Monteiro, J. Goré, *Tetrahedron Lett.* **1991**, *32*, 1641.

[20] I. Coudanne, J. Castro, G. Balme, *Synlett* **1998**, 995.

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