Tetrasubstituted Carbon Centers

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Copper/Titanium Catalysis Forms Fully Substituted Carbon Centers from the Direct Coupling of Acyclic Ketones, Amines, and Alkynes**

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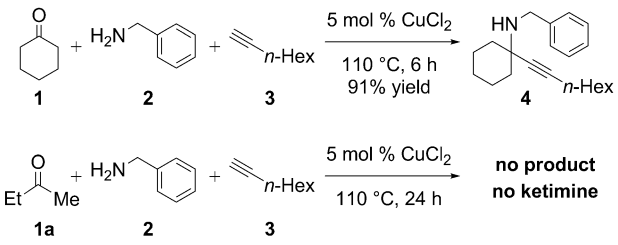
A wide range of natural products and bioactive compounds contain fully substituted carbon centers.[1] To circumvent the difficulty of creating these hindered C–N bonds in one step, compounds are commonly synthesized and rearrangement induced.[2] A catalytic system capable of overcoming the barrier to the condensation of a ketone and an amine to a ketimine, while leaving a nucleophile able to attack would lead to the direct formation of tetrasubstituted carbon atoms bearing amines.[3] In contrast to the wide array of three-component couplings (3CC) of aldehydes by the in situ formation of aldimines, reactions of ketones as electrophiles require an extra step that costs time, energy, and chemicals to produce and purify the ketimine starting material.[4] Dozens of enantioselective additions to ketimines have appeared without examples of the corresponding 3CC in either asymmetric or racemic form.[1] This situation suggests that the direct 3CC of ketones is more difficult to achieve than the asymmetric addition of nucleophiles to preformed ketimines.

The nucleophilic attack on imines by terminal alkynes has been widely studied owing to the intrinsic biological activity and utility of the resulting propargylamines as synthetic building blocks.[5] Aldehyde–amine–alkyne couplings (A^3) abound,[6–8] but as ketones are 750-times less-active than aldehydes as electrophiles,[9] the corresponding KA^2 procedure for unactivated ketones has not been reported. The three catalytic methods developed for cyclohexanones[10–12] rely on the fact that they undergo nucleophilic attack 300-times faster than acyclic ketones.[13] Cyclohexanone is a special case of near aldehyde-like reactivity,[14] and its corresponding ketimines[15] readily react to release torsional strain.[16]

Until Van der Eycken and co-workers described their solvent-free KA^2 methodology,[10] the catalytic incorporation of any ketone was an isolated, low-yielding event.[17] By applying microwave conditions in the presence of 20 mol% CuI, cyclohexanones and benzylamines couple with phenylacetylenes in 31–82% yield.[10] Employing 4 mol% $AuBr_3$, Ji and co-workers focused on cyclic amines and phenylacetylenes.[11] With 1 equivalent morpholine and 1.5 equivalents each of 2-pentanone and phenylacetylene, this Au^{III} system produces what they term a quaternary propargylamine in 54% yield.

We recently disclosed a green[18] copper(II)-catalyzed solvent-free KA^2 of cyclohexanone that uses 1:1:1 stoichiometry of the three coupling partners, such that the sole by-product is one equivalent of water.[12] Heating cyclohexanone (**1**), benzylamine (**2**), and 1-octyne (**3**) in with 5 mol% $CuCl_2$ produces the *N*-benzyl propargylamine **4** in 91% yield (Scheme 1). However, when cyclohexanone is replaced with



Scheme 1. Catalysts reported for cyclohexanone KA^2 cannot convert simple 2-butanone under the same conditions.

2-butanone (**1a**), neither ketimine intermediate nor the desired propargylamine product is observed under identical conditions (Scheme 1). Elevated temperatures, microwave conditions, and standard drying agents do not improve the reaction.[19] The conditions reported by Van der Eycken and Ji also fail. Thus, the KA^2 of acyclic ketones pose a serious synthetic challenge.

The catalytic cycle proposed for these types of reactions involves condensation of amine and carbonyl with subsequent attack of the resultant imine by the metal acetylide formed from the terminal alkyne.[6,7] We hypothesized that a more-active Lewis acid additive could overcome both the barrier to in situ ketimine formation and activate these less-reactive ketimines for subsequent attack. Ellman and co-workers and Davis et al. have demonstrated that the formation of aldimines can be facilitated by a range of Lewis acidic dehydrating agents.[20] However, their result showed that titanium (IV) ethoxide was unique in its ability to form ketimines without competitive aldol reactions. $Ti(OEt)_4$ is inexpensive and filtration removes the benign TiO_2 by-products.[20]

Exploration of Lewis acid additives began with the combination of 2-butanone (**1a**), benzylamine (**2**), and 1-octyne (**3**) which is unreactive under all known conditions (Scheme 1). Table 1 shows a range of Lewis acids tested in conjunction with 5 mol% $CuCl_2$. When added in a fraction of the 2 or 5 equivalents previously reported,[20] 50 mol% of

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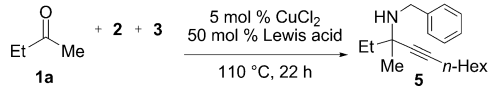
Table 1: Lewis acids tested for the conversion into propargylamine.



Entry	Lewis acid	GC yield [%][a]
1	**$Ti(OEt)_4$**	**92**
2	$Ti(OiPr)_4$	34
3	$AlCl_3$	0
4	$FeCl_3$	0
5	$AuCl_3$	0
6	$AuBr_3$	0

[a] Reaction conditions: neat with 1.0 mmol each of ketone, amine, and alkyne, $CuCl_2$ (0.05 mmol), and Lewis acid (0.5 mmol) under Ar; best result highlighted in bold.

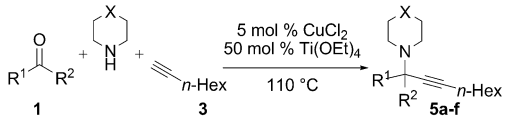
$Ti(OEt)_4$ or $Ti(OiPr)_4$ provide propargylamine **5** in 92% or 34% GC yield, respectively. Lewis acidic aluminum, iron, and gold sources tested induce no conversion from starting materials despite their utility in imine alkynylation.[7,11] Under an atmosphere of either air or N_2, propargylamine **5** forms cleanly but conversion halts at two-thirds that of the same reaction under Ar. Thus, heating ketone, amine, and alkyne with 5 mol% $CuCl_2$ and 50 mol% $Ti(OEt)_4$ produces the *N*-benzyl propargylamine **5** in 74% yield. The cooperative effect of both metals is required. In the absence of $Ti(OEt)_4$, the starting materials do not react. If copper is removed, ketimine forms in the presence of titanium but is not alkynylated.

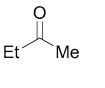
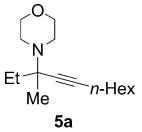
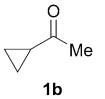
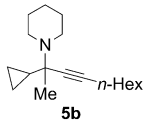
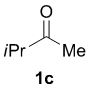
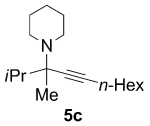
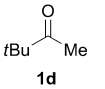
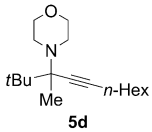
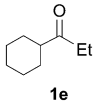
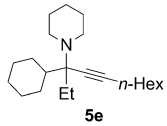
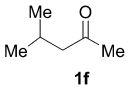
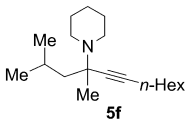
The simple method of heating equimolar amounts of ketone, amine, and alkyne with Cu^{II}/Ti^{IV} is successful for a variety of nonsymmetric ketones (Table 2). With 5 mol% $CuCl_2$ and 25 mol% $Ti(OEt)_4$, 2-butanone (**1a**) combines with morpholine and 1-octyne to give **5a** in 84% yield (entry 1). For most substrates, 25 mol% $Ti(OEt)_4$ is sufficient for conversion to product but 50 mol% provides higher yields.[19] Hindered pinacolone (**1d**) forms propargylamine **5d** where the new C–N bond bridges a tertiary amine and tetrasubstituted carbon with a vicinal quaternary carbon. However, aromatic ketones remain unreactive.[11]

Titanium appears to work cooperatively with copper to accelerate in situ imine formation and alkynylation. The rate of alkynylation of purified ketimine heated in the presence of 5 mol% $CuCl_2$ is half the rate of the direct KA^2 with 5 mol% $CuCl_2$ and 50 mol% $Ti(OEt)_4$.[19] As nonsymmetric ketones are utilized, all the products described herein are chiral. The first catalytic diastereoselective KA^2 was achieved using this new method (Scheme 2): 1*R*-(+)-camphor (**1g**), benzylamine (**2**), and 1-octyne (**3**) produce **5g** in 61% yield with over 95:5 diastereoselectivity as determined by ^1H NMR spectroscopy.[21]

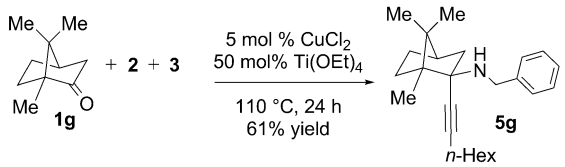
As shown in Table 3, terminal alkynes bearing aryl, alkyl, chlorinated, and cyano groups couple efficiently (71–91% yield). This contrasts with previous cyclohexanone KA^2 conditions in which utilizing alkyl alkynes reduces the product yield by half.[10,11] In addition to the synthetic utility of propargylamines,[5] the nitrile group of **6d** and the chloro group of **6e** (entries 4 and 5) can be readily converted into a variety of other functional groups. Note that these yields are achieved using equimolar amounts of the three coupling partners.

Table 2: Acyclic ketones form fully substituted C–N bonds.



Entry	Ketone **1**	*t* [d]	Product **5**	Yield [%][a]
1	 **1a**	2	 **5a**	84[b]
2	 **1b**	3	 **5b**	71
3	 **1c**	2	 **5c**	75
4	 **1d**	2	 **5d**	82
5	 **1e**	3	 **5e**	64[c]
6	 **1f**	3	 **5f**	82

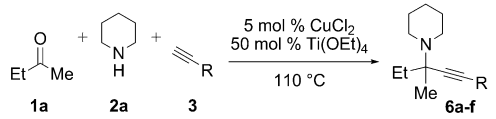
[a] Yield of isolated product under standard conditions: neat with 1:1:1 stoichiometry of ketone, amine, and alkyne (1.0 mmol each), $CuCl_2$ (0.05 mmol), and $Ti(OEt)_4$ (0.5 mmol) under Ar. [b] 0.25 mmol $Ti(OEt)_4$. [c] 1.0 mmol $Ti(OEt)_4$.



Scheme 2. Highly diastereoselective KA^2 reaction with camphor.

Table 4 displays the scope of the amine component of these KA^2 reactions. Propargylamines **6f** and **6g** from piperidine and morpholine provide 90% and 91% yields of tertiary amines attached to a fully substituted carbon center (Table 4, entries 1 and 2). While primary amines are considered to be difficult substrates compared to secondary amines,[10] aminomethyl naphthalene provides **6h**, with a free N–H moiety for derivatization. Bearing additional pharmacophores, *N*-propyl cyclopropylmethyl (**6i**) and *N*-

Table 3: A range of alkyl and aryl terminal alkynes react efficiently.

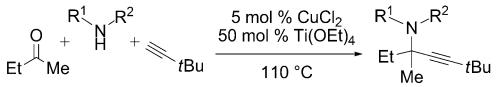


1a 2a 3 6a-f

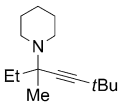
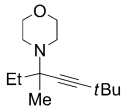
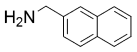
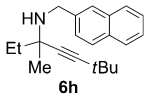
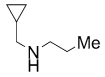
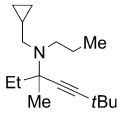
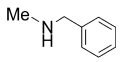
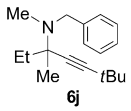
Entry	Propargylamine **6**	*t* [h]	Yield [%][a]
1	**6a**: R = *n*-Hex	48	85
2	**6b**: R = Ph	22	70
3	**6c**: R = $(CH_2)_3$Ph	72	71
4	**6d**: R = $(CH_2)_3$CN	48	76
5	**6e**: R = $(CH_2)_3$Cl	21	91
6	**6f**: R = *t*Bu	23	90

[a] Yield of isolated product under standard conditions: neat with 1:1:1 stoichiometry of ketone, amine, and alkyne (1.0 mmol each), $CuCl_2$ (0.05 mmol), and $Ti(OEt)_4$ (0.5 mmol) under Ar.

Table 4: Primary and secondary, cyclic and acyclic amines in KA^2.



1a 2 3a 6f-k

Entry	Amine	*t* [h]	Product	Yield [%][a]
1	 **2a**	23	 **6f**	90
2		23	 **6g**	91
3		22	 **6h**	73
4		48	 **6i**	73
5		23	 **6j**	81

[a] Yield of isolated product under standard conditions: neat with 1:1:1 stoichiometry of ketone, amine, and alkyne (1.0 mmol each), $CuCl_2$ (0.05 mmol), and $Ti(OEt)_4$ (0.5 mmol) under Ar.

methyl benzyl (**6j**) amines are accessed in 73% and 81% yield, respectively.

To our knowledge, this is the first method developed for the catalytic KA^2 of acyclic ketones. This method overcomes the barrier to reactivity for a broad range of unactivated ketones under solvent-free conditions and without the waste in terms of excess substrate[22] that often detracts from the advantages of multicomponent reactions.[23] Primary and secondary, cyclic and acyclic amines couple rapidly with nonsymmetric ketones and terminal alkynes to give secondary and tertiary *N*-propargylamines at tetrasubstituted carbon centers. Compared to current syntheses reliant on stoichiometric metal acetylide addition to ketimines,[5d] our approach provides a faster route to compounds with both therapeutic activity and utility in natural-product synthesis.[5] A highly diastereoselective example with camphor inspires our current efforts to make this KA^2 reaction enantioselective.

The cooperative effects of inexpensive titanium(IV) ethoxide and copper(II) chloride[24] catalyze in situ ketimine formation and activates the ketimine for alkynylation. Nucleophiles successful in 3CCs with aldehydes and amines lack the corresponding 3CC with ketones.[3–5] This unique Cu^{II}/Ti^{IV} system for the activation of ketone electrophiles may enable expansion to nucleophiles other than alkynes for direct access to a wide range of fully substituted carbon centers bearing amines.

Experimental Section

To an oven-dried test tube equipped with magnetic stir bar and Teflon-seal screw cap was added $CuCl_2$ (5 mol%) and $Ti(OEt)_4$ (50 mol%). The tube was purged with argon for 5 min. Ketone (1.0 mmol), alkyne (1.0 mmol), and amine (1.0 mmol) were added, and the reaction was stirred at 110°C for the indicated time. Upon reaction completion, as judged by GC, the mixture was cooled to room temperature and directly loaded onto a silica gel column and eluted with ethyl acetate in hexanes to afford the desired product.

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[1] a) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; b) M. Chavarot, J. J. Byrne, P. Y. Chavant, Y. Vallee, *Tetrahedron: Asymmetry* **2001**, *12*, 1147; c) S. Masumoto, H. Usuda, M. Suzuki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5634; d) N. Kato, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2004**, *45*, 3147; e) N. Kato, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2004**, *45*, 3153; f) R. Berger, K. Duff, J. L. Leighton, *J. Am. Chem. Soc.* **2004**, *126*, 5686; g) X. Huang, J. Huang, Y. Wen, X. Feng, *Adv. Synth. Catal.* **2006**, *348*, 2579; h) C. Lauzon, A. B. Charette, *Org. Lett.* **2006**, *8*, 2743; i) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7687; j) Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 500; k) R. Yazaki, T. Nitabaru, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 14477; l) Y. Du, L.-W. Xu, Y. Shimizu, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 16146; m) R. Shintani, M. Takeda, T. Tsuji, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 13168; n) R. Shintani, M. Takeda, Y.-T. Soh, T. Ito, T. Hayashi, *Org. Lett.* **2011**, *13*, 2977; o) T. Nishimura, A. Noishiki, G. C. Tsui, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 5056.

[2] J. Clayden, M. Donnard, J. Lefranc, D. J. Tetlow, *Chem. Commun.* **2011**, *47*, 4624.

[3] G. K. S. Prakash, T. Mathew, C. Panja, S. Alconcel, H. Vaghoo, C. Do, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 3703.

[4] S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* **2011**, *111*, 2626.

[5] a) B. Nilsson, H. M. Vargas, B. Ringdahl, U. Hacksell, *J. Med. Chem.* **1992**, *35*, 285; b) K. Hattori, M. Miyata, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 1151; c) M. A. Huffman, N. Yasuda, A. E. DeCamp, E. J. Grabowski, *J. Org. Chem.* **1995**, *60*, 1590; d) G. S. Kauffman, G. D. Harris, R. L. Dorow, B. R. P. Stone, R. L. Parsons, J. A. Pesti, N. A. Magnus, J. M. Fortunak, P. N. Confalone, W. A. Nugent, *Org. Lett.* **2000**, *2*, 3119; e) K. Kihara, T. Aoki, A. Moriguchi, H. Yamamoto, M. Maeda, N. Tojo, T. Yamanaka, M. Ohkubo, N. Matsuoka, J. Seki, S. Mutoh, *Drug Dev. Res.* **2004**, *61*, 233; f) J. C. Culhane, L. M. Szewczuk, X. Liu, G. Da, R. Marmorstein, P. A. Cole, *J. Am. Chem. Soc.* **2006**, *128*, 4536; g) N. Chernyak, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 2803; *Angew. Chem. Int. Ed.* **2010**, *49*, 2743; h) M. J. Albaladejo, F. Alonso, Y. Moglie, M. Yus, *Eur. J. Org. Chem.* **2012**, 3093, and references therein.

[6] For some early examples of racemic A^3 methods, see: a) S. Sakaguchi, T. Kubo, Y. Ishii, *Angew. Chem.* **2001**, *113*, 2602; *Angew. Chem. Int. Ed.* **2001**, *40*, 2534; b) C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268; c) C. Wei, C.-J. Li, *Green Chem.* **2002**, *4*, 39; d) J. H. Zhang, C. Wei, C.-J. Li, *Tetrahedron Lett.* **2002**, *43*, 5731; e) C. M. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584.

[7] For Reviews on imine alkynylation and A^3, see: a) G. Blay, A. Monleón, J. R. Pedro, *Curr. Org. Chem.* **2009**, *13*, 1498; b) W. J. Yoo, L. Zhao, C.-J. Li, *Aldrichimica Acta* **2011**, *44*, 43.

[8] a) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 2651; *Angew. Chem. Int. Ed.* **2002**, *41*, 2535; b) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763.

[9] J. P. Guthrie, *Can. J. Chem.* **1975**, *53*, 898.

[10] O. P. Pereshivko, V. A. Peshkov, E. V. Van der Eycken, *Org. Lett.* **2010**, *12*, 2638.

[11] M. Cheng, Q. Zhang, X.-Y. Hu, B.-G. Li, J.-X. Ji, A. S. C. Chan, *Adv. Synth. Catal.* **2011**, *353*, 1274.

[12] C. J. Pierce, C. H. Larsen, *Green Chem.* **2012**, *14*, 2672.

[13] E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Sausalito, CA, **2006**, p. 562.

[14] a) C. Fischer, E. M. Carreira, *Synthesis* **2004**, 1497; b) C. E. Meyet, C. J. Pierce, C. H. Larsen, *Org. Lett.* **2012**, *14*, 964.

[15] a) W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 4576; *Angew. Chem. Int. Ed.* **2004**, *43*, 4476; b) Y. Ma, E. Lobkovsky, D. B. Collum, *J. Org. Chem.* **2005**, *70*, 2335.

[16] a) M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, *9*, 2199; b) M. Chérest, H. Felkin, *Tetrahedron Lett.* **1968**, *9*, 2205.

[17] M. J. Aliaga, D. J. Ramon, M. Yus, *Org. Biomol. Chem.* **2010**, *8*, 43.

[18] R. Noyori, *Green Chem.* **2003**, *5*, G37.

[19] See Supporting Information for details on reaction optimization.

[20] a) G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 1278; b) F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli, H. Zhang, *J. Org. Chem.* **1999**, *64*, 1403.

[21] D. R. Brittelli, G. A. Boswell, *J. Org. Chem.* **1981**, *46*, 312.

[22] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197.

[23] a) A. Dömling, *Chem. Rev.* **2006**, *106*, 17; b) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439; c) J. E. Biggs-Houck, A. Younai, J. T. Shaw, *Curr. Opin. Chem. Biol.* **2010**, *14*, 371.

[24] Cost (in USD) of $AuBr_3$ ranges from \$71 g Strem Chemicals, Inc., to \$116 g from Sigma–Aldrich. $CuCl_2$ costs \$1 g from Sigma–Aldrich. $Ti(OEt)_4$ costs \$0.58 g from Strem.

