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Palladium/copper tandem catalysis for carbon–carbon triple bond cleavage of diaryl acetylenes

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ABSTRACT

A method for carbon–carbon triple bond cleavage based on palladium/copper tandem catalysis is developed. In this chemistry, anilines and diaryl acetylenes were converted into benzamides through cascade transformations combining palladium-catalyzed hydroamination of alkyne with copper-catalyzed aerobic oxidative C–C bond cleavage.

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Alkyne could be readily converted into many different compounds, such as aldehydes,¹ ketones,² diketones,³ alkenes,⁴ and triazoles,⁵ which makes this class of compounds widely used in organic synthesis as versatile building blocks.⁶ Recently, the transformations based on carbon–carbon triple bond cleavage have attracted considerable attention. Among them, alkyne metathesis is the one investigated mostly and deeply.⁷ However, other transformations that relied on the catalytic cleavage of the carbon–carbon triple bond still remain in a few examples.^{8–11} As a result, research on developing new methods for C≡C bond cleavage will no doubt enrich the potential application of alkyne in organic synthesis.

Tandem reaction that enables successive transformations without isolating relevant intermediates so as to minimize waste and increase efficiency has emerged as a hot research topic.¹² In 2002, Yamamoto reported a palladium-catalyzed intermolecular hydroamination of alkynes (Scheme 1),¹³ in which the hydroamination products, enamines, are unstable and tend to undergo hydrolysis, giving ketones as the final products. Combining with our recent work, a copper-catalyzed aerobic oxidative C–C bond cleavage of unstrained ketones with air and amines,^{14,15} we envisioned the palladium/copper tandem catalysis for carbon–carbon triple bond cleavage of alkyne for the synthesis of amide.¹⁶

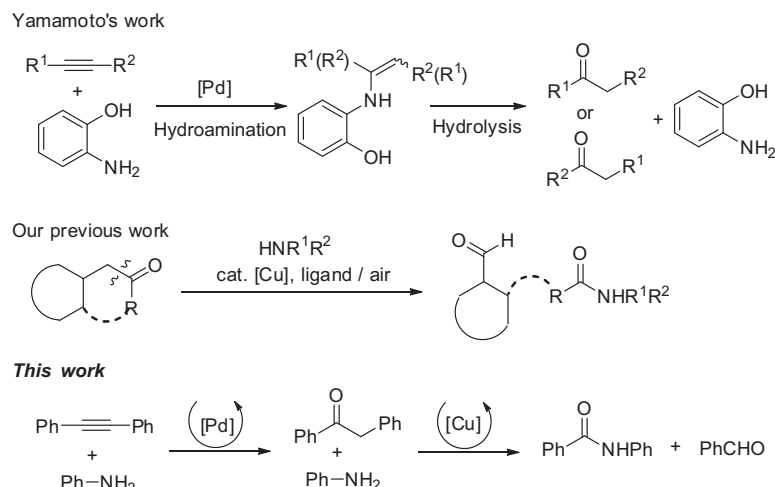
To test our hypothesis, the reaction of aniline (**1a**) and diphenylacetylene (**2a**) was carried out. After extensive screening

of reaction variables, the optimized conditions [PdCl₂ (10 mol %), CuCl₂·2H₂O (20 mol %), DPPE (10 mol %), 1,10-phenanthroline monohydrate (40 mol %), AgOTf (20 mol %), H₂O (5 equiv), and dioxane (0.25 mL), 100 °C, air, 24 h] were obtained. Under these conditions, carbon–carbon triple bond cleavage product **3aa** was isolated in 76% yield (Table 1, entry 1). Removing each of these necessary conditions from the standard, such as PdCl₂, CuCl₂·2H₂O, AgOTf, and H₂O will lead to the poor yields of this transformation (entries 2–5). On the other hand, carried out without using ligands, the transformation also became sluggish (entries 6 and 7). Compared with the negative impact of Cu(OAc)₂ instead of CuCl₂, Pd(OAc)₂ showed good catalytic effect instead of PdCl₂, giving **3aa** in comparable yield (entries 8 and 9). Notably, it proceeded smoothly in an oxygen atmosphere, while the reaction was completely thwarted in a nitrogen atmosphere. Moreover, the amount of solvent has a significant influence on yield (entry 15).

With the optimized conditions in hand, the substrate scope of amines was explored firstly. The transformation afforded products with *para*-, *meta*-, *ortho*-methyl substituents in moderate yields (Table 2, entries 2–5). Substrates with the halo group, such as fluoro, chloro, and bromo, were well-tolerated, giving the corresponding amides in moderate to good yields (entries 7–12). Notably, substrates with trifluoromethyl and cyano were also compatible (entries 13 and 14). However, no desired product was observed when 4-nitro aniline was employed (entry 15). In addition, the transformation delivered *N*-(naphthalen-2-yl) benzamide in good yield (entry 16).

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Scheme 1. Tandem catalysis for carbon–carbon triple bond cleavage.

Table 1
Examination of reaction conditions^a

$\text{Ph-NH}_2 + \text{Ph-C}\equiv\text{C-Ph} \xrightarrow[\text{dioxane (0.25 mL), 100 }^\circ\text{C, air}]{\text{PdCl}_2 \text{ (10 mol \%), DPPE (10 mol \%), CuCl}_2\cdot 2\text{H}_2\text{O (20 mol \%), 1,10-Phen-H}_2\text{O (40 mol \%), AgOTf (20 mol \%), H}_2\text{O (5 equiv)}} \text{Ph-C(=O)-NHPh}$		
1a	2a	3aa
Entry	Changes from the 'standard conditions'	Yield ^b (%)
1	None	79 (76)
2	No PdCl ₂	0
3	No CuCl ₂ ·2H ₂ O	0
4	No H ₂ O	0
5	No AgOTf	Trace
6	No DPPE	38
7	No 1,10-Phen·H ₂ O	57
8	Pd(OAc) ₂ instead of PdCl ₂	70
9	Cu(OAc) ₂ instead of CuCl ₂	66
10	DPPB instead of DPPE	44
11	DPPP instead of DPPE	70
12	AgOAc instead of AgOTf	0
13	N ₂ instead of air	0
14	O ₂ instead of air	75
15	The amount of dioxane was 1 mL	41

^a Standard conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), PdCl₂ (10 mol %), CuCl₂·2H₂O (20 mol %), DPPE (10 mol %), 1,10-phenanthroline monohydrate (40 mol %), AgOTf (20 mol %), H₂O (5 equiv), dioxane (0.25 mL), stirred at 100 °C under air for 24 h. DPPB = 1,4-bis(diphenylphosphino)butane; DPPE = 1,2-bis(diphenylphosphino)ethane; DPPP = 1,3-bis(diphenyl phosphino)propane.

^b GC-yields. The number in parentheses refers to the isolated yield.

Subsequently, the substrate scope of alkynes was explored (Table 3). Under the standard conditions, symmetric diaryl acetylenes with electron-donating or electron-withdrawing groups were tolerated, giving amides in moderate yields (entries 1–5). However, dibutyl acetylene did not work (entry 6). As for asymmetric diaryl acetylenes, amide mixtures were obtained (entries 7 and 9). It is worth noting that a single product was observed instead when acetylene **2i** was used (entry 8). Moreover, this catalytic system was ineffective for the carbon–carbon bond cleavage of methylphenyl acetylene (entry 10).

In the reaction mixture of aniline (**1a**) and diphenylacetylene (**2a**), GC–MS analysis did detect the formation of 1,2-diphenylethan-1-one (**4a**). To verify the tandem catalytic process of this transformation and unveil the reason that led to the poor yields

when 4-nitroaniline, dibutyl acetylene and methylphenyl acetylene were used, stepwise reactions were carried out. The results related to the first step, palladium-catalyzed hydroamination, and the second step, copper-catalyzed aerobic oxidative C–C bond cleavage, were summarized in Tables 4 and 5, respectively. First of all, when this tandem catalysis proceeded stepwisely, diphenyl acetylene (**2a**) could be converted into 1,2-diphenylethan-1-one (**4a**) in the presence of aniline (**1a**) at the first step (Table 4, entry 1) and 1,2-diphenylethan-1-one (**4a**) could be transformed into amide **3aa** at the second step indeed (Table 5, entry 1). Those results proved that the tandem catalytic process did work as we conceived and one-pot manipulation did lead to higher efficiency (Table 1, entry 1). Secondly, 4-nitroaniline (**1o**) could react with diphenyl acetylene (**2a**) to give 1,2-diphenylethan-1-one **4a** (Table 4, entry 2), but could not react with **4a** to give amide

Table 2
Substrate scope of amines^a

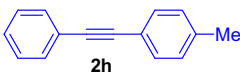
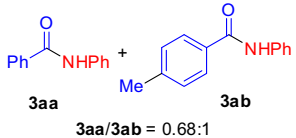
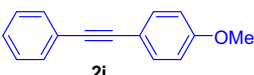
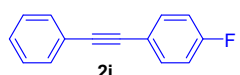
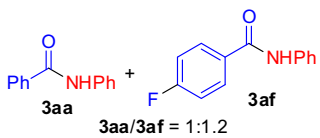
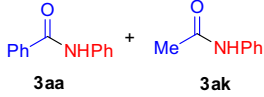
$\text{Aryl-NH}_2 + \text{Ph-C}\equiv\text{C-Ph} \xrightarrow[\text{dioxane (0.25 mL), 100 }^\circ\text{C, air}]{\text{PdCl}_2 \text{ (10 mol \%), DPPE (10 mol \%), CuCl}_2\cdot 2\text{H}_2\text{O (20 mol \%), 1,10-Phen-H}_2\text{O (40 mol \%), AgOTf (20 mol \%), H}_2\text{O (5 equiv)}} \text{Ph-C(=O)-NH-Aryl}$		
1	2a	3
Entry	Aryl	Yield ^b (%)
1	H	76 (3aa)
2	4-Methyl	71 (3ba)
3	3-Methyl	62 (3ca)
4	2-Methyl	55 (3da)
5 ^c	2,4,6-Trimethyl	63 (3ea)
6	3-Methoxy	40 (3fa)
7 ^c	4-Fluoro	81 (3ga)
8	4-Chloro	70 (3ha)
9	4-Bromo	80 (3ia)
10 ^c	2-Bromo	51 (3ja)
11	4-Iodo	50 (3ka)
12	3-Iodo	70 (3la)
13 ^c	4-Trifluoromethyl	47 (3ma)
14 ^c	4-Cyano	50 (3na)
15 ^c	4-Nitro	0 (3oa)
16		81 (3pa)

^a Standard conditions, see Table 1.

^b Isolated yield.

^c Reaction time was extended to 36 h.

Table 3
Substrate scope of alkynes^a

$\text{Ph-NH}_2 + \text{R}^1\text{C}\equiv\text{C}\text{R}^2 \xrightarrow[\text{dioxane (0.25 mL), 100 }^\circ\text{C, air}]{\text{PdCl}_2 \text{ (10 mol \%), DPPE (10 mol \%), CuCl}_2\cdot 2\text{H}_2\text{O (20 mol \%), 1,10-Phen}\cdot\text{H}_2\text{O (40 mol \%), AgOTf (20 mol \%), H}_2\text{O (5 equiv)}} \text{R}^1(\text{R}^2)\text{C(=O)NHPH}$			
Entry	Substrates	Products	Yield ^b (%)
1	R ¹ = R ² = <i>p</i> -Methylphenyl (2b)	3ab	47
2	<i>m</i> -Methoxyphenyl (2c)	3ac	55
3	<i>p</i> -Chlorophenyl (2d)	3ad	50
4	<i>m</i> -Fluorophenyl (2e)	3ae	56
5	<i>p</i> -Fluorophenyl (2f)	3af	72
6	<i>n</i> -Butyl (2g)	3ag	0
7 ^c		 3aa/3ab = 0.68:1	30 (3aa) 43 (3ab)
8			53
9 ^c		 3aa/3af = 1:1.2	28 (3aa) 33 (3af)
10			0

^a Standard conditions, see Table 1.^b Isolated yield.^c The ratio of the mixture was determined by ¹H NMR.**Table 4**
Palladium-catalyzed intermolecular hydroamination of alkyne^a

$\text{R}^1\text{-NH}_2 \text{ (1, 0.5 equiv)} + \text{R}^2\text{C}\equiv\text{CR}^3 \xrightarrow[\text{dioxane (0.25 mL), 100 }^\circ\text{C, air, 24 h}]{\text{PdCl}_2 \text{ (10 mol \%), DPPE (10 mol \%), AgOTf (20 mol \%), H}_2\text{O (5 equiv)}} \text{R}^2\text{C(=O)CH}_2\text{R}^3 \text{ or } \text{R}^3\text{C(=O)CH}_2\text{R}^2$				
Entry	R ¹	R ²	R ³	Product ^b
1	Phenyl	Phenyl	Phenyl	4a (43%)
2	4-Nitrophenyl	Phenyl	Phenyl	4a (18%)
3	Phenyl	<i>n</i> -Butyl	<i>n</i> -Butyl	4g (0%)
4	Phenyl	4-Methoxyphenyl	Phenyl	4i (22%), 4i' (0%)
5	Phenyl	Phenyl	Methyl	4k (56%), 4k' (0%)

^a Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), PdCl₂ (10 mol %), DPPE (10 mol %), AgOTf (20 mol %), H₂O (5 equiv), dioxane (0.25 mL), stirred at 100 °C under air for 24 h.^b Isolated yield based on alkyne **2**.

(Table 5, entry 2). Thirdly, the hydroamination of dibutyl acetylene with aniline was unfeasible (Table 4, entry 3). Next, palladium-catalyzed hydroamination furnished ketone **4i** and **4k** selectively when asymmetric alkyne **2i** and **2k** were employed, respectively (Table 4, entries 4 and 5). That reasons why single product **3ai** was obtained when alkyne **2i** was subjected to the standard

Table 5
Copper-catalyzed aerobic oxidative C–C bond cleavage of ketone^a

$\text{R}^1\text{-NH}_2 + \text{R}^2\text{C(=O)CH}_2\text{R}^3 \xrightarrow[\text{dioxane (0.25 mL), 100 }^\circ\text{C, air, 24 h}]{\text{CuCl}_2\cdot 2\text{H}_2\text{O (20 mol \%), 1,10-Phen}\cdot\text{H}_2\text{O (40 mol \%)}} \text{R}^2\text{C(=O)NHR}^1$				
Entry	R ¹	R ²	R ³	Product ^b
1	Phenyl	Phenyl	Phenyl	3aa (15%)
2	4-Nitrophenyl	Phenyl	Phenyl	3ao (0%)
3	Phenyl	<i>n</i> -Butyl	<i>n</i> -Butyl	3ga (0%)
4	Phenyl	Phenyl	Methyl	3aa (0%)

^a Reaction conditions: **1** (0.2 mmol), **4** (0.4 mmol), CuCl₂·2H₂O (20 mol %), 1,10-phenanthroline monohydrate (40 mol %), dioxane (0.25 mL), stirred at 100 °C under air for 24 h.^b Isolated yield.

conditions (Table 3, entry 8). Finally, 1-phenyl-1-propanone (**4k**) could not generate the amide at the second step, indicating that copper-catalyzed aerobic C–C bond cleavage is only effective to benzyl ketone (Table 5, entry 4). It is consistent with the result when alkyl ketone was used at the second step (Table 5, entry 3) as well as the result we previously reported.¹⁴

In conclusion, we have developed a tandem catalytic system for the cleavage of carbon–carbon triple bond. In this chemistry,

anilines and diaryl acetylenes were converted into benzamides through cascade transformations combining palladium-catalyzed hydroamination of alkyne with copper-catalyzed aerobic oxidative C–C bond cleavage. As far as we know, this is the first Letter of the transformation of this kind. Further studies on the synthetic applications of this method are ongoing in our group.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.08.020>.

References and notes

- Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121–1150; Oestreich, M. In *Science of Synthesis*; Brückner, R., Ed.; Thieme: Stuttgart, 2006; Vol. 25, pp 199–211.
- Figadère, B.; Franck, X. In *Science of Synthesis*; Cossy, J., Ed.; Thieme: Stuttgart, 2006; Vol. 26, pp 401–411.
- For reviews, see: Jacques, M. J. *Mol. Catal. A: Chem.* **2011**, 338, 7–17; Haines, A. H. *Methods for the Oxidation of Organic Compounds In Alkanes, Alkenes, Alkynes, and Arenes*; Academic Press: New York, 1985; For recent examples, see Xu, C.-F.; Xu, M.; Jia, Y.-X.; Li, C.-Y. *Org. Lett.* **2011**, 13, 1556–1559; Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. *Org. Lett.* **2009**, 11, 1841–1844; Wan, Z.-H.; Jones, C. D.; Mitchell, D.; Pu, J. Y.; Zhang, T. Y. *J. Org. Chem.* **2006**, 71, 826–828; Dayan, S.; Ben-David, I.; Rozen, S. J. *Org. Chem.* **2000**, 65, 8816–8818.
- For reviews, see: Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, 2001; Takaya, H.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 443.
- Reviews on click reaction, see: Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, 39, 1302–1315; Franck, A.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, 109, 4207–4220; Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, 108, 2952–3015; Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, 41, 2110–2113; Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, 40, 2004–2021; Huisgen, R. 1,3-Dipolar Cycloadditions—Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; p 267.
- Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, 104, 3079–3160; Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, 43, 3368–3398; Hudrlík, P. F.; Hudrlík, A. M. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1978; Vol. 1, pp 240–273; Rutledge, T. F. *Acetylenes and Allenes*; Reinhold Book Corporation: New York, 1969; Winterfeldt, E. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; p 267; Raphael, R. A. In *Acetylenic Compounds in Organic Synthesis*; Butterworths: London, 1955.
- For selected reviews, see: Villar, H.; Marcus, F.; Bolm, C. *Chem. Soc. Rev.* **2007**, 36, 55–66; Deshmukh, P. H.; Blechert, S. *Dalton Trans.* **2007**, 2479–2491; Zhang, W.; Moore, J. S. *Adv. Synth. Catal.* **2007**, 349, 93–120; Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307–2320.
- Shimada, T.; Yamamoto, Y. J. *Am. Chem. Soc.* **2003**, 125, 6646–6647.
- Datta, S.; Chang, C.-L.; Yeh, K.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, 125, 9294–9295.
- Wang, A.; Jiang, H. J. *Am. Chem. Soc.* **2008**, 130, 5030–5031; Liu, Y.; Song, F.; Guo, S. J. *Am. Chem. Soc.* **2006**, 128, 11332–11333.
- Shen, T.; Wang, T.; Qin, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, 52, 6677–6680.
- For some selected reviews, see: Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, 45, 1278–1293; Pellissier, H. *Adv. Synth. Catal.* **2012**, 354, 237–294; Zhou, J. *Chem. Asian J.* **2010**, 5, 422–434; Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564; Tietze, L. F. *Chem. Rev.* **1996**, 96, 115; Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, 96, 195–206; Bunce, R. A. *Tetrahedron* **1995**, 51, 13103–13103.
- Shimada, T.; Yamamoto, Y. J. *Am. Chem. Soc.* **2002**, 124, 12670–12671.
- Zhou, W.; Fan, W.; Jiang, Q.; Liang, Y.-F.; Jiao, N. *Org. Lett.* **2015**, 17, 2542–2545.
- For some reviews for C–C bond activation, see: Crabtree, R. H. *Nature* **2000**, 408, 415–416; Jun, C.-H. *Chem. Soc. Rev.* **2004**, 33, 610–618; Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, 14, 1–20; Muzart, J. *Tetrahedron* **2005**, 61, 9423–9463; Kondo, T.; Mitsudo, T. *Chem. Lett.* **2005**, 34, 1462–1467; Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, 79, 1315–1321; Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, 41, 222–234; Winter, C.; Krause, N. *Angew. Chem., Int. Ed.* **2009**, 48, 2460–2462; Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, 48, 2452–2456; Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, 7, 2835–2840; Murakami, M. *Chem. Rec.* **2010**, 10, 326–331; Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, 1100–1105; Dermenci, A.; Coe, J. W.; Dong, G. *Org. Chem. Front.* **2014**, 1, 567–581; C–C bond activation *Topics in Current Chemistry*; Dong, G., Ed.; Springer: Berlin, 2014; Vol. 346, Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, 114, 8613–8661; Liu, H.; Feng, M.; Jiang, X. *Chem. Asian J.* **2014**, 9, 3360–3382.
- For reviews on the application of amide, see: Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, 97, 2243–2266; Larock, R. C. *Comprehensive Organic Transformation*; VCH: New York, 1999; Guo, X.; Facchetti, A.; Marks, T. J. *Chem. Rev.* **2014**, 114, 8943–9021; He, B.; Pun, A. B.; Zhrebetskyy, D.; Liu, Y.; Liu, F.; Klivansky, L. M.; McGough, A. M.; Zhang, B. A.; Lo, K.; Russell, T. P.; Wang, L.; Liu, Y. J. *Am. Chem. Soc.* **2014**, 136, 15093–15101; He, B.; Pun, A. B.; Klivansky, L. M.; McGough, A. M.; Ye, Y.; Zhu, J.; Guo, J.; Teat, S. J.; Liu, Y. *Chem. Mater.* **2014**, 26, 3920–3927; He, B.; Dai, J.; Zhrebetskyy, D.; Chen, T. L.; Zhang, B. A.; Teat, S. J.; Zhang, Q.; Wang, L.; Liu, Y. *Chem. Sci.* **2015**, 6, 3180–3186.