

Commercial Supported Gold Nanoparticles Catalyzed Alkyne Hydroamination and Indole Synthesis

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Abstract: Commercial gold nanoparticle supported on TiO₂ was found to be a highly efficient catalyst for alkyne hydroamination. Terminal alkynes could easily undergo intermolecular hydroamination with low catalyst loading (0.2 mol% Au) under solvent-free conditions. Indoles were efficiently synthesized using microwave through intramolecular hydroamination.

Keywords: Au/TiO₂; hydroamination; indole; recyclable;

Nitrogen containing compounds such as amines and N-heterocycles are widely encountered in the scaffolds of various bioactive natural products, pharmaceuticals, and materials.^[1] Therefore, many methods such as reductive amination^[2] and C–N cross-coupling^[3] have emerged for their construction.^[4] Among these methods, hydroamination represents an atom-economical strategy because of the direct addition of amines to readily accessible alkenes, alkynes and allenes.^[5] On the one hand, intermolecular hydroamination affords structurally complex amines; on the other hand, intramolecular hydroamination provides access to a wide range of N-containing cyclic compounds. Various transition metal catalysts have proven their value in the hydroamination of alkynes,^[6] of which homogeneous cationic gold catalysis has attracted significant attention because of its excellent activity under mild reaction conditions.^[7] However, the non-recyclability of homogeneous gold catalysts and the decay of cationic gold greatly limited their application in organic synthesis.^[8] In this regard, heterogeneous gold catalysts, especially gold nanoparticles, are highly desirable in such transformation due to their stability and ease of manipulation.^[9]

Gold nanoparticles (Au/NPs) have been successfully applied in many organic reactions such as oxidation,^[10] reduction,^[11] hydrosilylation,^[12] and cross-coupling,^[13] but reports of Au/NPs mediated hydroamination, through π bond activation, are scarce.^[14] It is believed that the cationic gold species present in gold nanoparticles is responsible for the activation of the unsaturated bond (also see Figure S-2).^[15] Herein we are glad to report an alkyne hydroamination catalyzed by commercially available supported gold nanoparticles (Au/TiO₂). Through our methodology, a wide range of terminal alkynes were regioselectively converted to amines through intermolecular hydroamination, using molar fraction amounts of catalyst and no additional solvent; on the other hand, intramolecular hydroamination furnished indole derivatives in high yields.

We used the hydroamination of phenylacetylene **1a** with aniline **2a** as our model reaction (Table 1). When Au/TiO₂ (0.2 mol% Au) was utilized, the corresponding imine product **3a'** was obtained in 55% yield after 7 hours at 80 °C. Extending the reaction time to 24 hours led to only minor increase in yield (Table 1, entry 1). Higher temperatures did not increase the yield significantly (Table 1, entry 2). Inspired by homogeneous gold catalysis, we added acid promoters into the reaction. To our delight, all of the acid additives tested were able to facilitate the formation of **3a'** with similar efficiency (Table 1, entries 3-6). The easy-to-handle solid phosphotungstic acid was chosen as additive in our study. An attempt to achieve higher yield by increasing the temperature (100 °C) failed (Table 1, entry 7). A lower temperature (60 °C) furnished the desired product in 20% yield (Table 1, entry 8). Finally, when only the acid additive was used, or the support TiO₂ was used as catalyst, no imine product

was observed, underscoring the crucial role of gold nanoparticles (Table 1, entry 9 and 10).

With optimized conditions in hand, the substrate scope of intermolecular hydroamination was next evaluated (Table 2). Due to the instability of the

Table 1. Screening of Au/TiO₂ catalyzed intermolecular hydroamination.

| Entry | Au/TiO ₂ (mol% Au) | Additive (mol%) | T (°C) | Yield (%) ^a |
|-----------------|----------------------------------|--|--------|------------------------|
| 1 | 0.2 | - | 80 | 55 |
| 2 | 0.2 | - | 100 | 62 |
| 3 | 0.2 | HOTf (0.1%) | 80 | 88 |
| 4 | 0.2 | HNTf ₂ (0.1%) | 80 | 88 |
| 5 | 0.2 | HCTf ₃ (0.1%) | 80 | 83 |
| 6 | 0.2 | H ₃ PO ₄ ·12WO ₃ (0.1%) | 80 | 86 |
| 7 | 0.2 | H ₃ PO ₄ ·12WO ₃ (0.1%) | 100 | 71 |
| 8 | 0.2 | H ₃ PO ₄ ·12WO ₃ (0.1%) | 60 | 20 |
| 9 | - | H ₃ PO ₄ ·12WO ₃ (0.1%) | 80 | 0 |
| 10 ^b | - | H ₃ PO ₄ ·12WO ₃ (0.1%) | 80 | 0 |

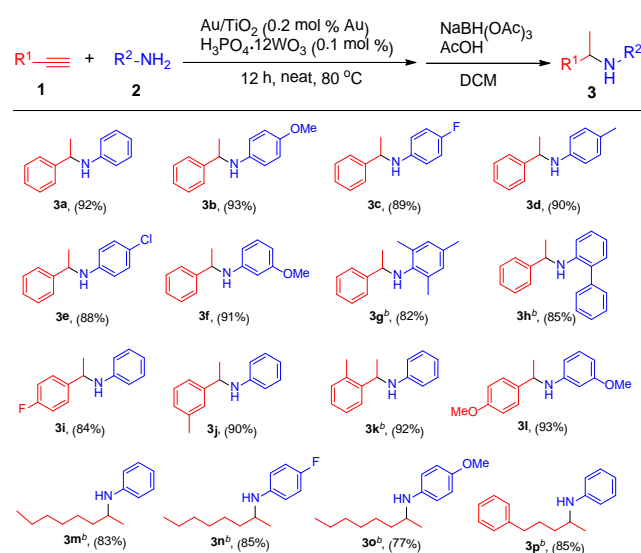
[a] Yields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

[b] TiO₂ (50 mol%) was used.

resulting imines, they were immediately reduced to amines after the reaction was completed. Both electron donating and electron withdrawing substituents on aniline were well tolerated (Table 2, 3a-3f). Anilines with substituents on sterically hindered positions (*o*-methyl and phenyl) could also provide the desired amines in high yields, although more catalyst and longer reaction time were required (Table 2, 3g-3h). The functional groups on phenylacetylene didn't affect the efficiency of the hydroamination (Table 2, 3i-3l). Harsher conditions were needed to achieve good yields when aliphatic alkynes were examined (Table 2, 3m-3p). Indole rings are one of the most ubiquitous and important heterocycles in nature.^[16] A plethora of methodologies exist for indole ring synthesis,^[17] but among them, the cycloisomerization of 2-alkynylanilines is the most straightforward and atom-economical. However, this straightforward synthesis of indoles hasn't received much attention using recyclable heterogeneous gold catalysts. The only reported work by Helaja and coworkers used homemade gold nanoparticles, which limits its application.^[18] Capitalizing on our success with intermolecular hydroamination of alkynes, we envisioned that commercially available Au/TiO₂ would enable the intramolecular version. Indeed, when microwave was applied, various 2-alkynylanilines were easily converted to the

corresponding indole derivatives. As shown in Table 3, different substituted 2-alkynylanilines furnished the corresponding indole products in very good to excellent yields (Table 3, 5a-5d). The halogens (F and Cl) and methyl group at the 4- or 5- position of aniline proved beneficial, allowing indole products to be

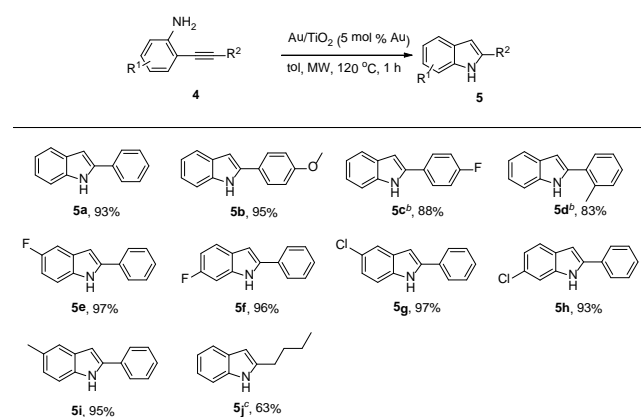
Table 2. Au/TiO₂ catalyzed intermolecular hydroamination of terminal alkynes.^[a]



[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Au/TiO₂ (0.2 mol% Au), H₃PO₄·12WO₃ (0.1 mol%), neat at 80 °C. Isolated yields were showed in parentheses.

[b] Au/TiO₂ (0.5 mol% Au), H₃PO₄·12WO₃ (0.5 mol%) were used in 24 h.

Table 3. Au/TiO₂ catalyzed indole synthesis through intramolecular hydroamination.^[a]



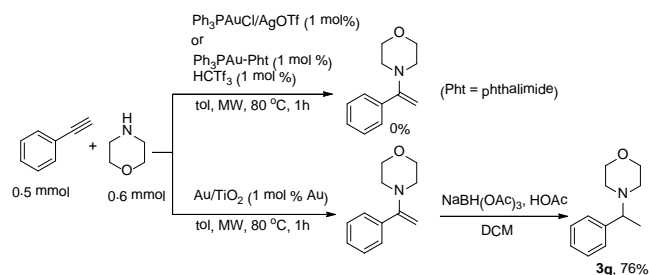
[a] Reaction conditions: **4** (0.1 mmol), Au/TiO₂ (5 mol% Au), in toluene (1 ml) at 120 °C for 1 h; Isolated yields. 140 °C.

[b] 140 °C.

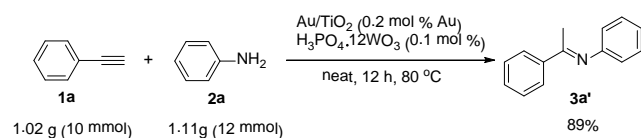
[c] H₃PO₄·12WO₃ (5 mol%) was used.

obtained in excellent yields (Table 3, **5e-5i**). When R² was replaced by an aliphatic group, an acid promoter was required (Table 3, **5j**).

The hydroamination of basic amines catalyzed by cationic gold is a challenge. This is because basic amine (e.g., morpholine) has much stronger affinity towards cationic gold than towards the alkyne substrate, thus, impairing the cationic gold.^[19] This is one reason why most homogeneous gold catalysts



Scheme 1. Comparison of homogeneous gold catalyst and gold nanoparticles in the hydroamination of basic amine.



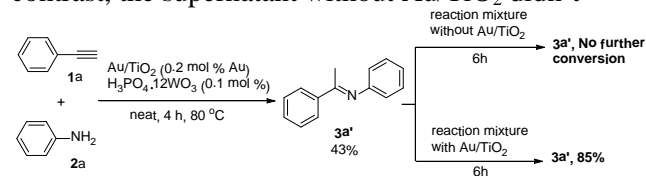
Scheme 2. Gram-scale intermolecular hydroamination of **1a** and **2a**.

cannot work in the strong basic environment created by basic amines.^[7c, 7d] We speculated that the cationic gold species present in Au/NPs might be more tolerant towards bases, and consequently, they could efficiently activate alkynes in the presence of basic amines. To examine this assumption, the hydroamination of phenylacetylene with morpholine was carried out using Au/TiO₂ as catalyst. To our delight, after reduction, the desired amine product was obtained in 76% yield. In contrast, a commonly used L-AuCl/AgOTf or an otherwise efficient imido gold pre-catalyst completely lost their activities in the presence of morpholine (Scheme 1).^[20] However, when thiomorpholine and pyrrolidine were used as basic amine partners, the hydroamination reaction didn't occur; piperidine gave low yield (25%) of imine product according to ¹H NMR. This result indicated that gold nanoparticles might be a better activator for triple bonds in the presence of some specific strong bases such as morpholine.

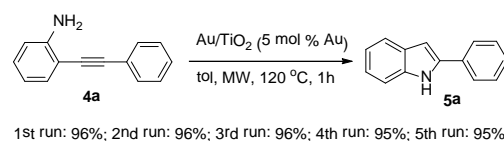
The scalability of the present method was also investigated through a gram-scale experiment (Scheme 2). The hydroamination proceeded smoothly, giving the corresponding imine product **3a'** in 89% yield.

A leaching experiment was also carried out (Scheme 3). The hydroamination of **1a** and **2a**

provided the desired imine **3a'** in 43% yield after 4 hours under the optimized conditions; then a portion of the supernatant (150 μ l) was transferred to another vial. Both the reaction mixture with Au/TiO₂ and the supernatant without Au/TiO₂ were allowed to react for another 2 hours. We found that the mixture containing Au/TiO₂ afforded **3a'** in 85% yield; In contrast, the supernatant without Au/TiO₂ didn't



Scheme 3. Leaching experiment of hydroamination with Au/TiO₂.



Scheme 4. Recyclability test of Au/TiO₂ in indole **5a** synthesis.

produce additional **3a'**. These results demonstrated that the hydroamination was catalyzed by gold species present in gold nanoparticles rather than species leached into solution.

The recyclability of gold nanoparticles was also investigated through five straight runs of cycloisomerization (Scheme 4). After each run Au/TiO₂ was filtered out and washed with fresh toluene. We found that gold nanoparticles were efficiently reused without loss of catalytic activity.

In conclusion, we have developed a highly efficient hydroamination protocol using commercially available gold nanoparticles (Au/TiO₂). Compared with commonly used homogeneous gold catalyst, this heterogeneous gold catalyst is cost-effective, easy-to-manipulate, and reusable. Au/TiO₂ catalyzed intermolecular hydroamination of terminal alkynes affording amines under solvent-free condition. What's more, a series of indole derivatives were synthesized through intramolecular hydroamination under microwave.

Experimental Section

General procedure for hydroamination of terminal alkynes **1** and anilines **2**

Au/TiO₂ (39.4 mg, 0.2 mol% Au) and H₃PO₄·12WO₃ (2.88 mg, 0.1 mol%) were placed in a dry and clean vial which was then vacuumed and purged with argon three times. Then a mixture of alkyne **1** (1 mmol) and aniline **2** (1.2 mmol) was added into the vial. The reaction mixture was stirred in oil bath at 80 °C for the designated time and

cooled down to room temperature. Then Au/TiO₂ was filtered, the residual was dissolved in DCM (6 ml). NaBH(OAc)₃ (424 mg, 2 eq.) and AcOH (114 μl, 2 eq.) were then added into the solution. The mixture was allowed to stir at room temperature for 24 hours. The reaction was quenched with 1M NaOH aqueous solution, extracted with DCM (5 ml × 2), combined organic phase was dried over Na₂SO₄, and after filtration of Na₂SO₄ the filtrate was concentrated to dryness and it was subjected to flash chromatography (silica gel; EA/hexane).

General procedure for indole 5 synthesis through cycloisomerization of 2-alkynylanilines 4

2-alkynylaniline **4** (0.1 mmol) was placed in a clean and dry microwave vial and dissolved in toluene (1 ml). Au/TiO₂ (98.5 mg, 5 mol% Au) was then added into the solution. The mixture reacted in microwave reactor for 1 hour at 120 °C and cooled down to room temperature. Then Au/TiO₂ was filtered, the filtrate was concentrated to dryness and subjected to flash chromatography (silica gel; EA/hexane).

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References

- [1] a) T. E. Muller, K. C. Hultsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795-3892; b) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611-1641.
- [2] a) S. Liang, P. Monsen, G. B. Hammond, B. Xu, *Org. Chem. Front.* **2016**, *3*, 505-509; b) H. Alinezhad, H. Yavari, F. Salehian, *Curr. Org. Chem.* **2015**, *19*, 1021-1049; c) S. Werkmeister, K. Junge, M. Beller, *Green Chem.* **2012**, *14*, 2371-2374.
- [3] a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534-1544; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27-50.
- [4] a) R. N. Salvatore, C. H. Yoon, K. W. Jung, *Tetrahedron* **2001**, *57*, 7785-7811; b) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753-819; c) B. Li, J.-B. Sortais, C. Darcel, *RSC Adv.* **2016**; d) C.-V. T. Vo, J. W. Bode, *J. Org. Chem.* **2014**, *79*, 2809-2815; e) B. Zhang, A. Studer, *Chem. Soc. Rev.* **2015**, *44*, 3505-3521; f) S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009-3019.
- [5] a) J. Bahri, B. Jamoussi, A. van Der Lee, M. Taillefer, F. Monnier, *Org. Lett.* **2015**, *17*, 1224-1227; b) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407-1420; c) J. C. H. Yim, J. A. Bexrud, R. O. Ayinla, D. C. Leitch, L. L. Schafer, *J. Org. Chem.* **2014**, *79*, 2015-2028; d) E. Kumaran, W. K. Leong, *Organometallics* **2015**, *34*, 1779-1782; e) R. Sarma, D. Prajapati, *Chem. Commun.* **2011**, *47*, 9525-9527; f) X. Xu, X. Zhang, Z. Wang, M. Kong, *RSC Adv.* **2015**, *5*, 40950-40952; g) J. C. H. Yim, L. L. Schafer, *Eur. J. Org. Chem.* **2014**, *2014*, 6825-6840; h) M. A. Chilleck, L. Hartenstein, T. Braun, P. W. Roesky, B. Braun, *Chem. Eur. J.* **2015**, *21*, 2594-2602; i) Z. L. Palchak, D. J. Lussier, C. J. Pierce, H. Yoo, C. H. Larsen, *Adv. Synth. Catal.* **2015**, *357*, 539-548; j) C. Brahm, P. Tholen, W. Saak, S. Doye, *Eur. J. Org. Chem.* **2013**, *2013*, 7583-7592; k) J. Bahri, R. Blicke, B. Jamoussi, M. Taillefer, F. Monnier, *Chem. Commun.* **2015**, *51*, 11210-11212; l) Q.-A. Chen, Z. Chen, V. M. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 8392-8395; m) R. Blicke, J. Bahri, M. Taillefer, F. Monnier, *Org. Lett.* **2016**, *18*, 1482-1485; n) J. A. Gurak, K. S. Yang, Z. Liu, K. M. Engle, *J. Am. Chem. Soc.* **2016**, *138*, 5805-5808.
- [6] L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* **2015**, *115*, 2596-2697.
- [7] a) V. Lavallo, J. H. Wright, F. S. Tham, S. Quinlivan, *Angew. Chem. Int. Ed.* **2013**, *52*, 3172-3176; b) X. Zeng, G. D. Frey, R. Kinjo, B. Donnadieu, G. Bertrand, *J. Am. Chem. Soc.* **2009**, *131*, 8690-8696; c) H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov, X. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 12100-12102; d) K. D. Hesp, M. Stradiotto, *J. Am. Chem. Soc.* **2010**, *132*, 18026-18029; e) A. Leyva, A. Corma, *Adv. Synth. Catal.* **2009**, *351*, 2876-2886; f) W. Debrouwer, T. S. A. Heugebaert, B. I. Roman, C. V. Stevens, *Adv. Synth. Catal.* **2015**, *357*, 2975-3006; g) D. Ye, J. Wang, X. Zhang, Y. Zhou, X. Ding, E. Feng, H. Sun, G. Liu, H. Jiang, H. Liu, *Green Chem.* **2009**, *11*, 1201-1208; h) L. Wang, L. Kong, Y. Li, R. Ganguly, R. Kinjo, *Chem. Commun.* **2015**, *51*, 12419-12422; i) Y. Zhang, J. P. Donahue, C.-J. Li, *Org. Lett.* **2007**, *9*, 627-630; j) A. Couce-Rios, G. Kovács, G. Ujaque, A. Lledós, *ACS Catal.* **2015**, *5*, 815-829; k) E. Mizushima, T. Hayashi, M. Tanaka, *Org. Lett.* **2003**, *5*, 3349-3352; l) S. Cai, K. Yang, D. Z. Wang, *Org. Lett.* **2014**, *16*, 2606-2609.
- [8] M. Kumar, J. Jasinski, G. B. Hammond, B. Xu, *Chem. Eur. J.* **2014**, *20*, 3113-3119.
- [9] a) M. Stratakis, H. Garcia, *Chem. Rev.* **2012**, *112*, 4469-4506; b) B. S. Takale, M. Bao, Y. Yamamoto, *Org. Biomol. Chem.* **2014**, *12*, 2005-2027; c) A. Corma, H. Garcia, *Chem. Soc. Rev.* **2008**, *37*, 2096-2126; d) Y. Zhang, X. Cui, F. Shi, Y. Deng, *Chem. Rev.* **2012**, *112*, 2467-2505.
- [10] a) J. Restrepo, R. Porcar, P. Lozano, M. I. Burguete, E. García-Verdugo, S. V. Luis, *ACS Catal.* **2015**, *5*, 4743-4750; b) S. Yudha S, I. Kusuma, N. Asao, *Tetrahedron* **2015**, *71*, 6459-6462.
- [11] a) A. Corma, P. Serna, *Science* **2006**, *313*, 332-334; b) Y. S. Wagh, N. Asao, *J. Org. Chem.* **2015**, *80*, 847-851; c) F.-Z. Su, L. He, J. Ni, Y. Cao, H.-Y. He, K.-N. Fan, *Chem. Commun.* **2008**, 3531-3533; d) L. He, L.-C. Wang, H. Sun, J. Ni, Y. Cao, H.-Y. He, K.-N. Fan, *Angew. Chem. Int. Ed.* **2009**, *48*, 9538-9541; e) E. Vasilikogiannaki, I. Titilas,

- G. Vassilikogiannakis, M. Stratakis, *Chem. Commun.* **2015**, 51, 2384-2387.
- [12] a) I. N. Lykakis, A. Psyllaki, M. Stratakis, *J. Am. Chem. Soc.* **2011**, 133, 10426-10429; b) I. Titilas, M. Kidonakis, C. Gryparis, M. Stratakis, *Organometallics* **2015**, 34, 1597-1600.
- [13] a) J. Han, Y. Liu, R. Guo, *J. Am. Chem. Soc.* **2009**, 131, 2060-2061; b) S. Carrettin, J. Guzman, A. Corma, *Angew. Chem. Int. Ed.* **2005**, 44, 2242-2245; c) A. Moragues, F. Neațu, V. I. Pârvulescu, M. D. Marcos, P. Amorós, V. Michelet, *ACS Catal.* **2015**, 5, 5060-5067.
- [14] a) L.-C. Lee, Y. Zhao, *ACS Catal.* **2014**, 4, 688-691; b) J. Zhao, Z. Zheng, S. Bottle, A. Chou, S. Sarina, H. Zhu, *Chem. Commun.* **2013**, 49, 2676-2678; c) H. Kitahara, H. Sakurai, *Chem. Lett.* **2012**, 41, 1328-1330; d) A. Corma, P. Concepción, I. Domínguez, V. Forné, M. J. Sabater, *J. Catal.* **2007**, 251, 39-47.
- [15] a) A. Goguet, M. Ace, Y. Saih, J. Sa, J. Kavanagh, C. Hardacre, *Chem. Commun.* **2009**, 4889-4891; b) L. K. Ono, B. Roldan Cuenya, *J. Phys. Chem. C* **2008**, 112, 4676-4686; c) L. Fu, N. Q. Wu, J. H. Yang, F. Qu, D. L. Johnson, M. C. Kung, H. H. Kung, V. P. Dravid, *J. Phys. Chem. B* **2005**, 109, 3704-3706; d) M. Boronat, P. Concepción, A. Corma, *J. Phys. Chem. C* **2009**, 113, 16772-16784; e) J. C. Fierro-Gonzalez, B. C. Gates, *Chem. Soc. Rev.* **2008**, 37, 2127-2134.
- [16] a) M.-Z. Zhang, Q. Chen, G.-F. Yang, *Eur. J. Med. Chem.* **2015**, 89, 421-441; b) V. Sharma, P. Kumar, D. Pathak, *J. Heterocycl. Chem.* **2010**, 47, 491-502; c) G. Bartoli, R. Dalpozzo, M. Nardi, *Chem. Soc. Rev.* **2014**, 43, 4728-4750.
- [17] a) Y. Yamane, X. Liu, A. Hamasaki, T. Ishida, M. Haruta, T. Yokoyama, M. Tokunaga, *Org. Lett.* **2009**, 11, 5162-5165; b) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, 67, 7195-7210; c) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, 106, 2875-2911; d) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, 105, 2873-2920; e) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, 4, 29-41.
- [18] J. E. Perea-Buceta, T. Wirtanen, O.-V. Laukkanen, M. K. Mäkelä, M. Nieger, M. Melchionna, N. Huittinen, J. A. Lopez-Sanchez, J. Helaja, *Angew. Chem. Int. Ed.* **2013**, 52, 11835-11839.
- [19] a) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, 49, 5232-5241; b) W. Wang, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2012**, 134, 5697-5705.
- [20] J. Han, N. Shimizu, Z. Lu, H. Amii, G. B. Hammond, B. Xu, *Org. Lett.* **2014**, 16, 3500-3503.

COMMUNICATION

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