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COMMUNICATION

Facile One-Pot Synthesis of 2-Aminoindoles from Simple Anilines and Ynamides

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A highly effective and straightforward one-pot synthesis of diversely substituted 2-aminoindoles has been developed, involving sequential Au(I)-catalyzed regioselective hydroamination and $CuCl_2$-mediated oxidative cyclization. This protocol offers an operationally easy, simple, robust, and sustainable approach with the use of readily available starting materials, good functional group tolerance, and high practicality and efficiency.

Among indoles referred to as "privileged structures," 2-aminoindoles are important structural motifs found in a wide range of bioactive compounds.[1] While numerous methods for construction of indoles have been developed, synthetic methods to produce 2-aminoindoles have remained limited. In recent years, various synthetic approaches toward 2-aminoindoles using ynamides[2] as versatile building blocks have been developed.[3-7] Ynamides are useful precursors as a source of either the N1 atom or C2-amino substituent for regioselective formation of the 2-aminoindole scaffold.

In 2003, Witulski and co-workers reported a Pd-catalyzed annulative cross-coupling reaction of *N*-(*o*-haloaryl)ynamides with primary and secondary amines as a source of the C2-amino substituent to afford 2-aminoindoles through a one-pot C-N/C-C bond forming sequence (Scheme 1A).[3a] Later, leading researchers in gold catalysis, Ye,[3b] Liu,[3c] and Hashmi[3d] independently demonstrated Au-catalyzed intermolecular reactions of ynamides with various nitrene transfer reagents (azides, benzisoxazoles, sulfilimines, respectively) as precursors of α-imino gold carbene intermediates as well as a source of C2-amino substituent, relying on the same bond disconnection approach. One of the most common synthetic strategies for 2-aminoindole synthesis is use of ynamides as a source of C2-amino substituents and C2 building blocks (C2-C3 bond) for the pyrrole nucleus of indoles (Scheme 1B). Some examples of Pd- and/or Cu-catalyzed one-pot processes involving *in situ* formation of *o*-aminoaryl-substituted ynamides (**A**) as a common intermediate have been reported (Scheme 1Ba).[4]

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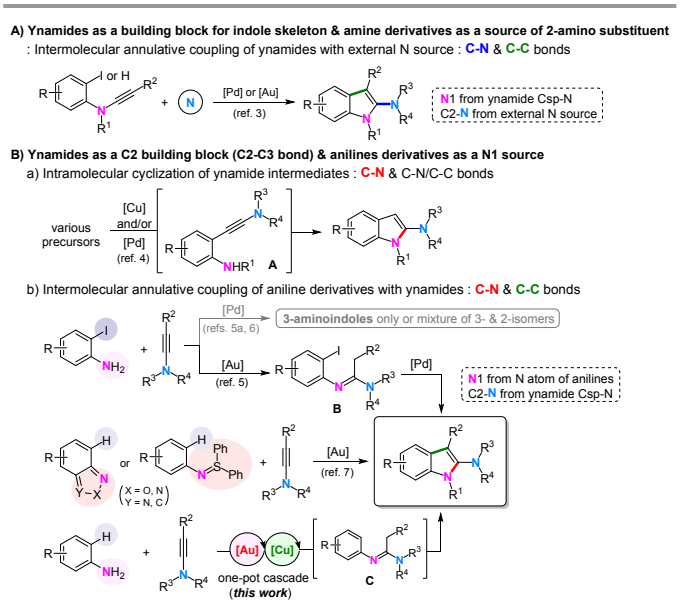
Common limitations of these methods include requisite use of prefunctionalized arenes and generation of only 3-unsubstituted indoles. On the other hand, Skrydstrup and co-workers developed a two-step process consisting of 1) Au-catalyzed hydroamination of ynamides with 2-haloanilines and 2) Pd-catalyzed cyclization of the so-generated amidine precursors (**B**) for synthesis of 2-amidoindoles (Scheme 1Bb, upper).[5a] This cyclization step required purified intermediates; thus, an attempt to perform a one-pot reaction directly using ynamides and 2-haloanilines failed. Interestingly, however, they found that the Pd-catalyzed Larock indole protocol gave a mixture of 2- and 3-aminoindole isomers with opposite regioselectivity, which has been wisely utilized for synthesis of δ-carbolines from ynamides and 2-haloanilines through Pd-catalyzed sequential reactions by Cao and Lai.[6] As a one-step protocol, Au-catalyzed intermolecular reactions of ynamides with various nitrene transfer reagents have been employed for sequential C-N and C-C bond formation (Scheme 1Bb, middle),[7] which is mechanistically similar but based on a different bond disconnection from that shown in Scheme 1A. In this reaction, *N*-heterocycles such as anthranils, benzotriazoles, and



Scheme 1 Synthesis of 2-aminoindoles employing ynamides.

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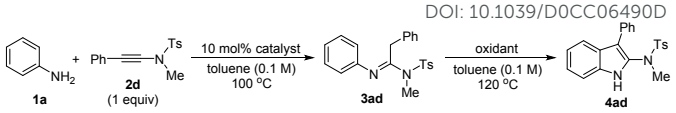
benzofurazan *N*-oxides used as nitrene transfer reagents provide indole products, which have a certain substituent such as acyl,[7a] pyrazolyl,[7b] and nitro[7c-d] group, respectively, mostly at the C7 position. In contrast, Hashmi successfully utilized sulfilimines as a nitrene transfer reagent with a traceless leaving group (i.e., sulfide) to afford diversely substituted 2-aminoindoles.[7f] Despite significant advances, several drawbacks such as requirement of prefunctionalized substrates and, thus, several steps or limited commercially available reagents for preparation of starting materials, use of costly ligands, and a stepwise process limit the practicality of these reactions. Therefore, development of a simple, cost-effective, and sustainable protocol for regioselective formation of such compounds is highly desirable. The use of low cost, diverse, and widely available anilines would be more efficient and attractive to improve the practicality and synthetic utility of this transformation.

Considering the regioselective reactivity of ynamides[2] and inspired by literature precedents of oxidative cyclization of *N*-aryl enamines[8a-d]/imines[8e] for indole synthesis, we envisaged regioselective addition of anilines to ynamides and subsequent oxidative cyclization of the ensuing amidines (**C**) to afford 2-aminoindoles (Scheme 1Bb, lower). Realization of this proposal would be a significant advance, providing a straightforward route to such compounds, overcoming the aforementioned deficiencies of the precedent syntheses.

As part of our continued interest in oxidative annulation and one-pot reactions in heterocycle synthesis,[9] we herein report a highly effective and facile synthesis of diversely substituted 2-aminoindoles directly from anilines and ynamides (Scheme 1Bb, lower). This one-pot sequential process consists of 1) C-N bond formation through Au(I)-catalyzed regioselective hydroamination of ynamides with anilines and 2) C-C bond formation through $CuCl_2$-mediated cyclization of the so-generated amidine intermediates.

To test the viability of the one-pot sequential process in forming 2-aminoindoles, **1a** and **2d** were employed as test substrates to investigate the stepwise hydroamination and oxidative cyclization reactions (Table 1).[10] First, we examined a variety of Brønsted/Lewis acids for hydroamination to form amidines **3**. Although most of the catalysts surveyed promoted hydroamination to give **3ad** in low to moderate yields, the combination of PPh_3AuCl and Ag salts such as $AgNTf_2$ or AgOTf was most effective for this transformation (entries 7-8).[5, 11] Having identified successful conditions for amidine formation, oxidative annulation of **3ad** was investigated under previously reported conditions for related processes of *N*-aryl enamines.[8] After initial findings that the desired indole product **4ad** was formed in 45% yield under Liang's protocol using $FeCl_3$ as a catalyst and $Cu(OAc)_2{\cdot}CuCl_2$ complex as an oxidant,[8c] further examination of the reaction parameters was undertaken. We found that a comparable yield of **4ad** could be obtained using only $CuCl_2$ (entry 9). Hoping to improve the reactivity as well as to examine compatibility with this cyclization condition, a variety of metal catalysts, including those that could promote the 1st step, were subjected to the $CuCl_2$-mediated reaction of **3ad**. Unfortunately, the presence of other metal catalysts

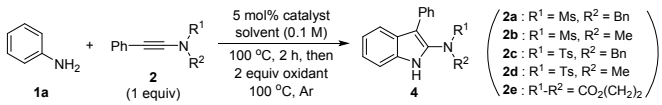
Table 1. Optimization studies: Stepwise process



Step 1 : Hydroamination			**Step 2** : Oxidative annulation		
Entry	Catalyst	**3ad** (%)[a]	Entry	Oxidant (equiv)	**4ad** (%)[a]
1	$HNTf_2$	55	9	$CuCl_2$ (3)	39
2	AgOTf	63	10	$Cu(OAc)_2$ (3)	trace
3	$ZnBr_2$	71[b]	11	CuI (3)	0
4	$CuCl_2$	31	12	I_2 (3) or NIS (3)	20 or 24
5	$Cu(OTf)_2$	71	13	NCS (1)	27
6	PPh_3AuCl	38	14[d]	$CuCl_2$ (2)	34
7	$PPh_3AuCl/AgNTf_2$[c]	93[b]	15[d-e]	$CuCl_2$ (2)	5-21
8	$PPh_3AuCl/AgOTf$[c]	90[b]	16[d, f]	$CuCl_2$ (2)	73[b]

[a] ^1H NMR yields. [b] Isolated yields. [c] 5 mol% each ([Au]:[Ag] = 1:1). [d] At 100 °C. [e] In the presence of 10 mol% $AgSbF_6$, $Cu(OTf)_2$, $FeCl_3$, or PPh_3AuCl/ AgOTf (1/1). [f] Using **3aa** (derived from **2a**) instead of **3ad** and isolated yield of **4aa**.

Table 2. Optimization studies: One-pot domino process[a]



Entry	**2**	Catalyst[a]	Oxidant	Solvent	Time (h)[b]	Yield (%)[c]
1	**2a**	$PPh_3AuCl/AgOTf$	$CuCl_2$	toluene	4	(60) (**4aa**)
2	**2a**	$PPh_3AuCl/AgNTf_2$	$CuCl_2$	toluene	4	(45)
3	**2a**	AgOTf	$CuCl_2$	toluene	10	17
4	**2a**	$Cu(OTf)_2$	$CuCl_2$	toluene	3	2
5	**2a**	$PPh_3AuCl/AgOTf$	I_2	toluene	2	6
6	**2a**	$PPh_3AuCl/AgOTf$	NIS	toluene	2	12
7	**2a**	$PPh_3AuCl/AgOTf$	NCS[d]	toluene	6	30
8	**2a**	$PPh_3AuCl/AgOTf$	$CuCl_2$	DCE	4	(44)
9	**2a**	$PPh_3AuCl/AgOTf$	$CuCl_2$	DMF	4	13
10	**2a**	$PPh_3AuCl/AgOTf$	$CuCl_2$	THF	4	(73)
11	**2b**	$PPh_3AuCl/AgOTf$	$CuCl_2$	THF	6	35 (**4ab**)
12	**2c**	$PPh_3AuCl/AgOTf$	$CuCl_2$	THF	6	(69) (**4ac**)
13	**2d**	$PPh_3AuCl/AgOTf$	$CuCl_2$	THF	6	30 (**4ad**)
14	**2e**	$PPh_3AuCl/AgOTf$	$CuCl_2$	THF	6	- (**4ae**)
15[e]	**2a**	$PPh_3AuCl/AgOTf$	$CuCl_2$	THF	24	12

Reaction conditions: **1a** (1 equiv), **2** (1 equiv), 5 mol% catalyst in solvent (0.1 M) at 100 °C for 2 h under Ar. Subsequently, oxidant (2 equiv) was added to the reaction mixture and stirred at 100 °C under Ar. [a] [Au]:[Ag] = 1:1. [b] Reaction time after the addition of oxidant. [c] Determined by ^1H NMR. Values in parentheses indicate isolated yields. [d] Using 1 equiv NCS. [e] All the catalysts, oxidant, and reagents were added at the outset of the reaction.

exerted a deleterious effect on the reaction (entries 14 vs. 15). A substantial effect of *N*-substituents of amidines was observed in the oxidative cyclization reaction, and *N*-benzyl-*N*-mesyl-substituted amidines (e.g., **3aa**) proved to be optimal (entry 16). Having established optimal conditions for the stepwise process, we investigated a one-pot domino reaction (Table 2).[10] Considering the preliminary results regarding the detrimental effect of metal catalysts including Au(I) on oxidative annulation, the presence of Au(I) in the same reaction vessel could influence the outcome of the 2nd step due to compatibility issues. Very

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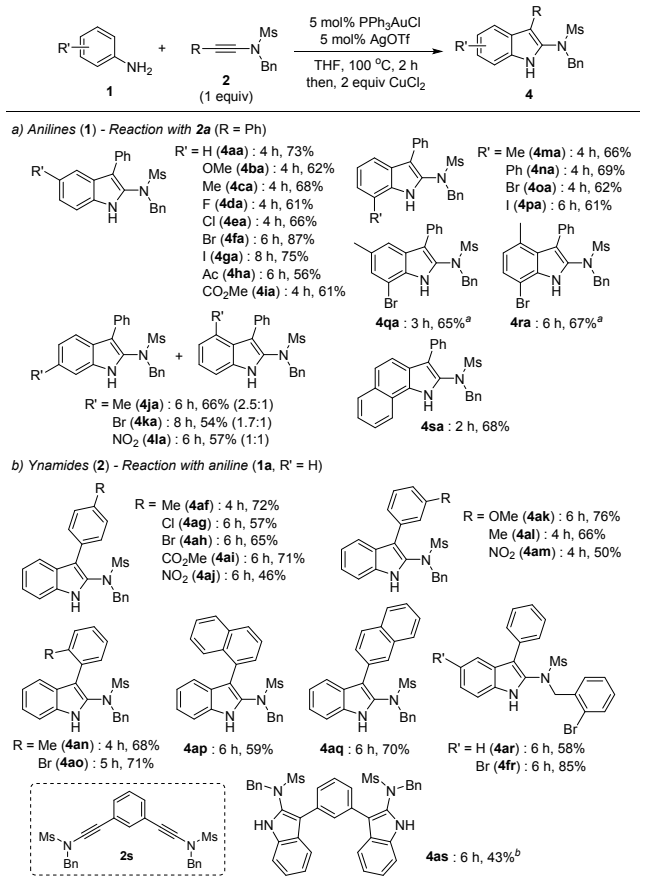
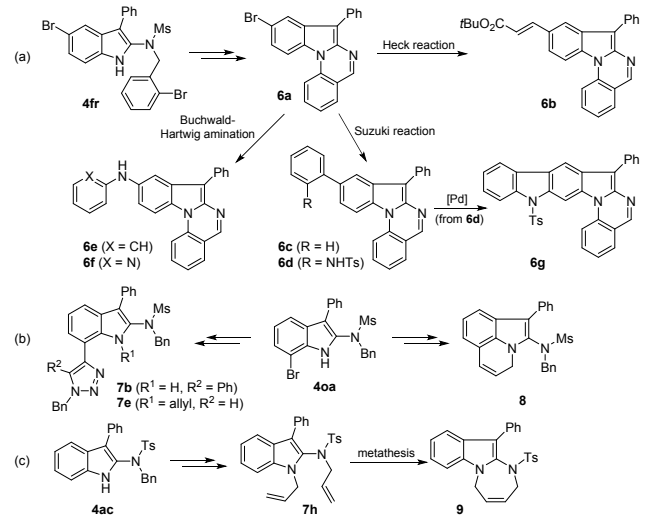


Scheme 2 Substrate scope. Reaction conditions: **1** (1 equiv), **2** (1 equiv), 5 mol% PPh_3AuCl, 5 mol% AgOTf in THF (0.1 M) at 100 °C for 2 h under Ar. Subsequently, $CuCl_2$ (2 equiv) was added to the reaction mixture and stirred at 100 °C for the provided time under Ar. Isolated yields are given. *a* After 3 h, $CuCl_2$ was added. *b* Using 2.1 equiv **1a**, 1 equiv **2s**, and twice amount of catalysts and reagents.

interestingly, in sharp contrast to the stepwise reaction, the 2nd step, $CuCl_2$-mediated cyclization, proceeded smoothly in the presence of the Au(I) catalyst used in the 1st step (entry 1). To find the optimal conditions for this sequence, diverse variations of the reaction parameters were explored. In this one-pot process, AgOTf and THF were more effective than $AgNTf_2$ and toluene as Ag salt and solvent, respectively (entries 1-2 and 10). Replacing any component with alternatives significantly reduced the conversion and efficiency (entries 1-9 vs. entry 10). For ynamide, benzyl (Bn) and mesyl (Ms) were identified as optimal *N*-substituents (entry 10 vs. entries 11-14). Encouraged by these results, we attempted this reaction by adding all the catalysts and reagents into the same pot from the outset; however, a low yield of **4aa** was obtained (entry 15). In contrast to related prior work,[5-6] the one-pot reaction successfully achieved regioselective construction of 2-aminoindoles directly from ynamides and simple anilines.

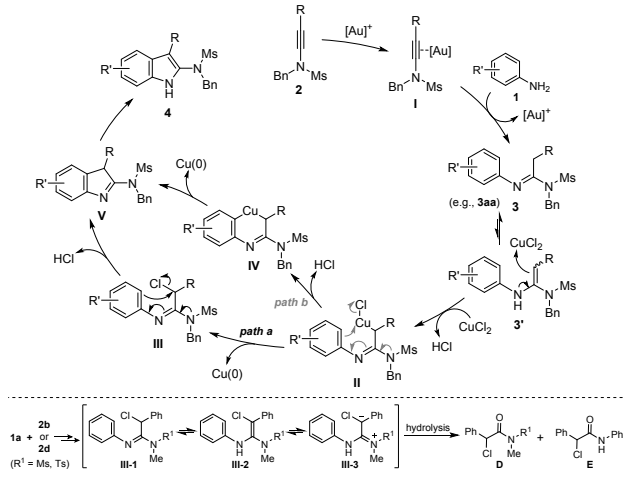
With establishment of a viable one-pot reaction system, we set out to explore the scope of this domino process. A wide range of anilines (**1**) underwent domino amidine formation/oxidative cyclization smoothly to afford the corresponding 2-aminoindoles (**4**) in good yields irrespective of the electronic properties and position of substituents (Scheme 2a). In general, a variety of aryl-substituted ynamides (**2**) was well tolerated regardless of substituent position, while strongly electron-withdrawing substituents, such as NO_2, resulted in relatively lower yields of the desired products (**4aj**, **4am**) (Scheme 2b). Furthermore, reaction of bis(ynamide) **2s** proceeded uneventfully to afford the desired bisindole **4as**. In contrast, the reaction failed with heteroaryl- and alkyl-substituted ynamides. This process can tolerate various functional groups such as halogen, ketone, ester, and nitro groups. In particular, both 2-haloanilines (**1o**-**r**→**4oa**-**ra**) and 2-haloaryl-substituted ynamides (**2o**→**4ao**, **2r**→**4ar**/**4fr**) afforded products with an intact halogen substituent. This functional group tolerance could be advantageous compared to other transition metal-catalyzed synthetic methods to prepare 2-aminoindoles[3a, 5-6] and makes this method particularly appealing, since it should permit further elaboration and enable greater structural diversity.



Scheme 3 Synthetic application.

To highlight the synthetic utility of this one-pot reaction, further transformation of the indoles obtained from this process was undertaken.[10] First, intramolecular *N*-arylation of **4fr**, which has an *ortho*-bromo substituent on the *N*-benzyl group, proceeded smoothly to give indoloquinazoline **6a** (Scheme 3a).[4c] Further elaboration of bromo-substituted **6a** was readily accomplished through Heck (**6b**), Suzuki (**6c**-**d**), and Buchwald-Hartwig amination (**6e-f**) reactions, leading to diversely substituted indoloquinazolines **6b-f** in good yields. Subsequent Pd-catalyzed oxidative C-H amidation of **6d** successfully installed the carbazole skeleton to afford **6g** in 91% yield. 7-Bromo-substituted **4oa** was transformed into 7-triazole-substituted indole **7b** or **7e** via Sonogashira reaction followed by Ru- or Cu-catalyzed cycloaddition of the so-generated 7-alkynyl indoles with benzyl azide (Scheme 3b). In addition, pyrroloquinoline **8** was constructed by *N*-allylation of **4oa** followed by Heck-type cyclization. In addition, facile removal of the *N*-Bn group led to NH-free indole, which could be transformed into **7h** by bisallylation. **7h** was further subjected to a metathesis reaction to form diazepinoindole **9** in 96% yield (Scheme 3c).

Although clearly detailed mechanistic studies are needed to clarify the mechanism especially for the Cu-mediated



Scheme 4 Proposed mechanism.

annulation step, a plausible mechanism for this one-pot reaction is proposed as outlined in Scheme 4. By analogy with mechanisms established for related Au(I)-catalyzed hydroamination of ynamides with anilines,[5, 11] amidine intermediate **3** is formed by the reaction of **1** and **2**. **3'** resulting from tautomerization of **3** undergoes electrophilic attack by $CuCl_2$ to provide **II** with loss of HCl. Reductive elimination followed by intramolecular nucleophilic attack by the *ortho* carbon of the aniline moiety to the chlorinated αC atom of intermediate **III** leads to the formation of **V** (path a). Subsequent isomerization of **V** produces the final product **4**. Alternatively, **IV** could be formed through nucleophilic attack of the *ortho* carbon of the aniline moiety of **II** to Cu,[8a-b,e] which is promoted by the electron-donating effect of the amide (-NMsBn) group (path b). The indole product **4** is generated by reductive elimination followed by isomerization of the resulting **V**. In the case of reactions with ynamides **2b** and **2d**, formation of α-chlorinated amides **D** and **E** was observed,[10] which might form via hydrolysis of the tautomers **III-1** and **III-3**, respectively. These findings suggest that this reaction more likely proceeds through path a, involving intermediate **III**.

In summary, we have developed a highly efficient and facile one-pot reaction for the synthesis of diversely substituted 2-aminoindoles from anilines and ynamides. In this one-pot sequential process, the two metal salts, Au(I) and $CuCl_2$, operate in two distinct reactions in series. To the best of our knowledge, this represents the first example using simple anilines as a N1 source for the pyrrole nucleus of indoles, offering new and straightforward access to synthetically valuable 2-aminoindoles.

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Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) J. Landwehr, S. George, E.-M. Karg, D. Poeckel, D. Steinhilber, R. Troschuetz, and O. Werz, *J. Med. Chem*., 2006, **49**, 4327; (b) M. Tichy, R. Pohl, H. Y. Xu, Y. L. Chen, F. Yokokawa, P. Y. Shi, and M. Hocek, *Bioorg. Med. Chem.*, 2012, **20**, 6123.

2 Selected reviews: (a) G. Evano, A. Coste, and K. Jouvin, *Angew. Chem. Int. Ed.,* 2010, **49**, 2840; (b) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064; (c) R. H. Dodd, and K. Cariou, *Chem. Eur. J.*, 2018, **24**, 2297.

3 (a) B. Witulski, C. Alayrac, and L. Tevzadze-Saeftel, *Angew. Chem. Int. Ed.*, 2003, **42**, 4257; (b) C. Shu, Y.-H. Wang, B. Zhou, X.-L. Li, Y.-F. Ping, X. Lu, and L.-W. Ye, *J. Am. Chem. Soc.*, 2015, **137**, 9567; (c) M.-H. Tsai, C.-Y. Wang, A. S. K. Raj, and R.-S. Liu, *Chem. Commun.*, 2018, **54**, 10866; (d) X. Tian, L. Song, M. Rudolph, F. Rominger, and A. S. K. Hashmi, *Org. Lett.*, 2019, **21**, 4327.

4 (a) P.-Y. Yao, Y. Zhang, and R. P. Hsung, K. Zhao, *Org. Lett.*, 2008, **10**, 4275; (b) K. Dooleweerdt, T. Ruhland, and T. Skrydstrup, *Org. Lett.*, 2009, **11**, 221; (c) S. E. Kiruthika, and P. T. Perumal, *Org. Lett.*, 2014, **16**, 484.

5 (a) S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer, and T. Skrydstrup, *Org. Lett.*, 2009, **11**, 4208; (b) D. Liu, Q. Nie, R. Zhang, and M. Cai, *Adv. Synth. Catal.*, 2018, **360**, 3940.

6 J. Cao, Y. Xu, Y. Kong, Y. Cui, Z. Hu, G. Wang, Y. Deng, and G. Lai, *Org. Lett.*, 2012, **14**, 38.

7 (a) H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger, and A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2016, **55**, 794; (b) D. Allegue, J. González, S. Fernández, J. Santamarıá, and A. Ballesteros, *Adv. Synth. Catal.*, 2019, **361**, 758; (c) W. Xu, Y. Chen, A. Wang, and Y. Liu, *Org. Lett.*, 2019, **21**, 7613; (d) C. Zhu, L. Kou, and X. Bao, *Chin. J. Chem.*, 2020, **38**, 57; (e) X. Tian, L. Song, K. Farshadfar, M. Rudolph, F. Rominger, T. Oeser, A. Ariafard, and A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2020, **59**, 471; (f) X. Tian, L. Song, M. Rudolph, F. Rominger, T. Oeser, and A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2019, **58**, 3589. Related intramolecular reactions: (g) W.-B. Shen, Q. Sun, L. Li, X. Liu, B. Zhou, J.-Z. Yan, X. Lu, and L.-W. Ye, *Nat. Commun.*, 2017, **8**, 1748.

8 (a) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, and F. Glorius, *Angew. Chem. Int. Ed.*, 2008, **47**, 7230; (b) R. Bernini, G. Fabrizi, A. Sferrazza, and S. Cacchi, *Angew. Chem. Int. Ed.*, 2009, **48**, 8078; (c) Z.-H. Guan, Z.-Y. Yan, Z.-H. Ren, X.-Y. Liu, and Y.-M. Liang, *Chem. Commun.*, 2010, **46**, 2823; (d) W. Yu, Y. Du, and K. Zhao, *Org. Lett.*, 2009, **11**, 2417; (e) Y. Wei, I. Deb, and N. Yoshikai, *J. Am. Chem. Soc.*, 2012, **134**, 9098.

9 (a) S. W. Youn, and E. M. Lee, *Org. Lett.*, 2016, **18**, 5728; (b) S. W. Youn, and Y. H. Kim, *Org. Lett.*, 2016, **18**, 6140; (c) S. W. Youn, T. Y. Ko, and Y. H. Jang, *Angew. Chem. Int. Ed.*, 2017, **56**, 6636; (d) S. W. Youn, and H. J. Yoo, *Adv. Synth. Catal.*, 2017, **359**, 2176; (e) S. W. Youn, T. Y. Ko, Y. H. Kim, and Y. A. Kim, *Org. Lett.*, 2018, **20**, 7869; (f) S. W. Youn, H. J. Yoo, E. M. Lee, and S. Y. Lee, *Adv. Synth. Catal.*, 2018, **360**, 278; (g) H. J. Yoo, and S. W. Youn, *Org. Lett.*, 2019, **21**, 3422.

10 For details, see the Supporting Information.

11 (a) X. Zhao, X. Song, H. Jin, Z. Zeng, Q. Wang, M. Rudolph, F. Rominger, and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2018, **360**, 2720; (b) N. D. Rode, A. Arcadi, A. Di Nicola, F. Marinelli, and V. Michelet, *Org. Lett.*, 2018, **20**, 5103; (c) R. Vanjari, S. Dutta, M. P. Gogoi, V. Gandon, and A. K. Sahoo, *Org. Lett.*, 2018, **20**, 8077.