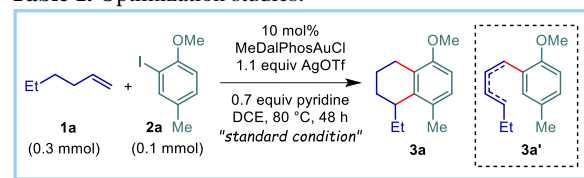


transformation underscores the unique reactivity profile offered by gold catalysis compared to other transition metals (Scheme 1b-c vs Scheme 1d).

At the outset, we chose 1-hexene **1a** and 2-iodo-1-methoxy-4-methylbenzene **2a** as coupling partners to validate our hypothesis (Table 1). After performing preliminary screening of reaction conditions,¹⁷ we found that the reaction between **1a** and **2a** in the presence of MeDalPhosAuCl (10 mol%), AgOTf (1.1 equiv), and pyridine (0.7 equiv) in DCE (0.1 M) at 80 °C for 12 h of stirring delivered annulation product **3a** along with the regioisomeric mixture of aryl alkenes **3a'** in 60% combined yield (entry 1 in the parenthesis). With the intuition that prolonging the reaction time might promote the conversion of aryl alkene intermediates (**3a'**) exclusively into the desired annulation product **3a**, the reaction was stirred for 48 hours. Pleasingly, this led to an enhanced yield of 78% for **3a** (entry 1). Further, deviation from the standard reaction conditions i.e. screening of silver salts (entries 2-4), bases (entries 5-6), and solvents (entries 7-8) had a detrimental effect on the reaction outcome.

Table 1. Optimization studies.^{[a],[b]}



Entry	Variation of the "standard condition"	Isolated yield (%)
1	none	78 (60 ^{[a],[b]})
2	AgNTf ₂ was used instead of AgOTf	64
3	AgBF ₄ was used instead of AgOTf	50 ^[b]
4	AgSbF ₆ was used instead of AgOTf	15 ^[b]
5	K ₃ PO ₄ was used instead of pyridine	52 ^[b]
6	2,6-lutidine was used instead of pyridine	56
7	<i>o</i> -DCB was used instead of DCE	60
8	CHCl ₃ was used instead of DCE	28 ^[b]

^[a]Reaction time 12 h. ^[b]Product **3a** along with the regioisomeric mixture of aryl alkenes **3a'**.

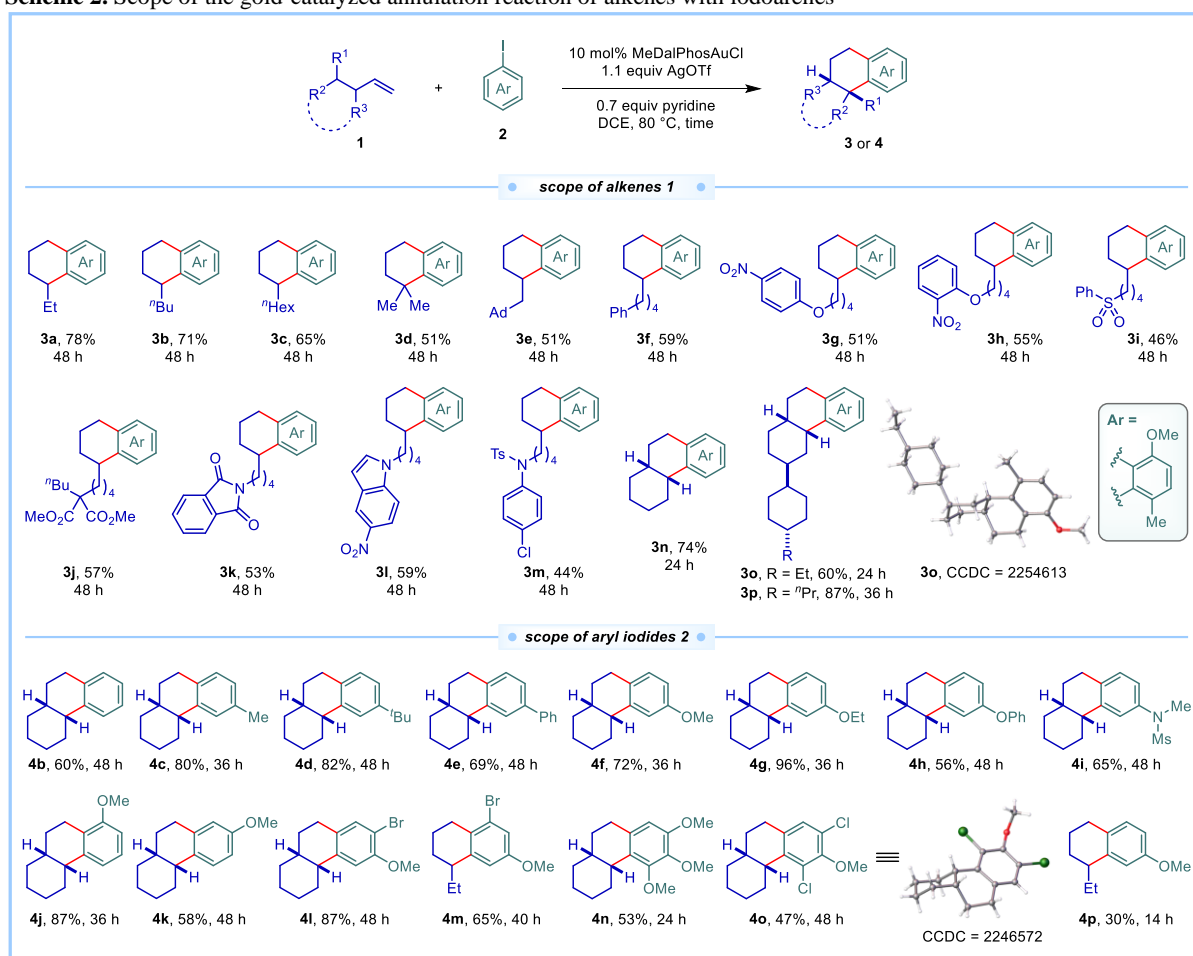
Having identified the optimal condition, we examined the scope of alkenes **1** by using 2-iodo-1-methoxy-4-methylbenzene **2a** as a model substrate (Scheme 2). To our delight, a wide range of alkenes **1a-1p** reacted smoothly to afford the desired cyclized products **3a-3p** in up to 87% yield. For instance, alkenes **1b-1f** reacted smoothly under the standard reaction conditions to afford the corresponding products **3b-3f** in 51-71% yield. Besides, the alkene tethered with phenoxide groups reacted with **2a** to afford the desired product **3g** and **3h** in 51% and 55% yield, respectively. Furthermore, the alkene tethered with sulfone, dimethyl malonates, phthalimide, indole, and protected aniline also reacted smoothly with **2a** to deliver the products **3i-3m** in 44-59% yield. Notably, a single *cis*-diastereomer of product **3n** was obtained in 74% yield when 1-vinyl-cyclohexane

was used as an alkene source. Additionally, 4-substituted-1-vinyl-cyclohexane derivatives (**1o-1p**) also reacted efficiently to deliver the desired products **3o-3p** in 60-87% yield as a single diastereomer. Next, we turned our attention to the scope of aryl iodides **2** (Scheme 2). Gratifyingly, a series of aryl iodides (**2b-2p**) having different substituents at *ortho*, *meta*, and *para* positions reacted smoothly to deliver the products **4b-4p** in up to 96% yield as a single *cis*-diastereomer. For instance, iodobenzene (**2b**) reacted smoothly under standard reaction conditions to deliver the desired product **4b** in 60% yield. Besides, *para*-substituted aryl iodides (**2c-2h**) reacted efficiently to afford the products **4c-4h** in 56-96% yield. Further, mesyl-protected *para*-iodo-*N*-methylaniline **2i** also reacted nicely to deliver the product **4i** in 65% yield. Moreover, the products **4j** and **4k** were obtained in 87% and 58% yield when *ortho*-iodoanisole (**2j**) and *meta*-iodoanisole (**2k**) were used as substrates. Additionally, *para*-iodoanisole bearing halo (Br, Cl) or electron-donating substituents also reacted smoothly under the standard reaction conditions, furnishing the corresponding products **4l-4o** in 47-87% yield with excellent chemoselectivity for the C(sp²)-I bond over other C(sp²)-X bonds (X = Br, Cl.; see entries **4l**, **4m**, **4o**).

Interestingly, when the simple alkenes were replaced with appropriately substituted aryl alkenes **1q-1r**, we observed the formation of 1,3-diarylation products **5a-5e** and 1,3-hydroarylation products **6a-6b** instead of regular annulation products (Scheme 3). This suggests that the allylic Heck products generated in the reaction could be directly intercepted by the tethered aryl ring to afford the observed products (*cf.* **III**).

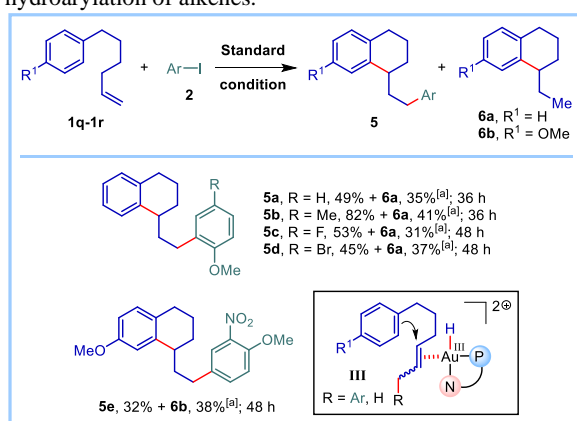
A few mechanistic investigations were carried out to gain a deeper understanding of the reaction mechanism (Scheme 4). To begin, time-dependent experiments were performed to understand the plausible intermediates for the formation of products **3** or **4**. In particular, when alkene **1a** was treated with **2f** under the standard reaction conditions, the allylic Heck product **7** was obtained in 80% yield in just 2 h;¹⁷ however, prolonged reaction time (14 h) resulted in the formation of **4p** in 30% yield (Scheme 4a). Similarly, when alkenes **1n** and **1p** were reacted with aryl iodides **2**, the chain-walking products **8a-8d** were formed in 51-65% yield in 2-12 h;¹⁹ while, further extending the reaction time to 36-48 h resulted in the formation of cyclized products **4f**, **4l**, and **4o** in 72%, 87%, and 47% yields, respectively (Scheme 4b). These control experiments (Schemes 4a and 4b) suggest that the allylic Heck product **7** and the chain-walking product **8** serve as intermediates in the formation of products **3** or **4**. Next, when the deuterated alkene **1o-D** was treated with **2f** in the presence of MeDalPhosAuCl (1 equiv) and AgOTf (2 equiv), the product **8e-D** was obtained in 54% yield (Scheme 4c). The migration of deuterium from the C1 (80% D) to C2 (64% D) position in product **8e-D** suggests that the chain-walking process is operative. Further, the alkene **1s-D** provided deuterium scrambling product **6c-D** in 44% yield (Scheme 4c). The scrambling of deuterium (0.15 D at C3 and 0.30 D at C2) and loss of D at C1 (1.35 H) in the product clearly suggests that the chain-walking process is operational. Furthermore, the formation of 1,*n*-hydroarylated products **6a-6c** (Scheme 3b) and incorporation of deuterium at the C3 position (0.15 D) in product **6c-D** (Scheme 4c) indicates that the chain-walking process follows a dissociative pathway. Additionally, the *cis* ring fusion in compounds **3** and **4** (Scheme 2) implies the π -activation mechanism.

Scheme 2. Scope of the gold-catalyzed annulation reaction of alkenes with iodoarenes^{[a],[b]}



^[a]Reaction conditions: 0.6 mmol **1**, 0.2 mmol **2**, 0.02 mmol MeDalPhosAuCl, 0.22 mmol AgOTf, 0.14 mmol pyridine, DCE (0.1 M), 80 °C.
^[b]Isolated yields.

Scheme 3. Gold-catalyzed 1,3-diarylation and 1,3-hydroarylation of alkenes.

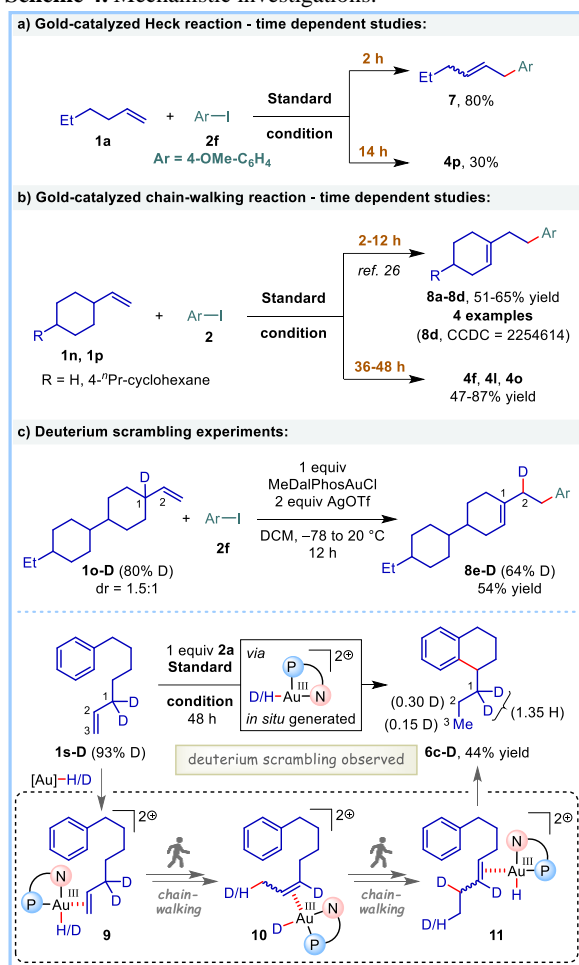


^[a]Yield calculated with respect to alkene.

To support the proposed mechanism,¹⁹ DFT computations were performed with the Gaussian 16 set of program using 1-vinyl-cyclohexane and 4-iodoanisole as model substrates (Figure 1).¹⁹ The study revealed that insertion of the alkene into the Au–Ar bond requires 14.8 kcal/mol free energy of activation (**TS_{AB}**) and is exergonic by 7.1 kcal/mol. As discussed in our previous study,¹⁷ the

resulting complex **B** shows a κ^1 -C coordination between gold and the *ipso* aryl carbon, making the benzylic hydrogen inaccessible for a *cis* β -H elimination. Lengthening of the *ipso*C–Au distance followed by β -H elimination resulted in the formation of the alkene complex **D** (-18.5 kcal/mol) through **TS_{BD}** (-3.4 kcal/mol). Next, the insertion of the alkene moiety into the Au–H bond can provide the agostic complex **E** (-16.5 kcal/mol) through **TS_{DE}** (-13.0 kcal/mol). Lengthening of the Au–H distance revealed **TS_{EF}** (-8.6 kcal/mol), leading to the non-agostic complex **F** (-14.2 kcal/mol). Flipping of the chair *via* **TS_{FG}** (-11.3 kcal/mol) proved necessary to reach the agostic complex **G** (-15.9 kcal/mol). The endocyclic alkene complex **H** (-17.8 kcal/mol) could be connected to **G** after β -H elimination through **TS_{GH}** (-13.9 kcal/mol). Back-flipping of the pseudo-chair *via* **TS_{HI}** (-12.1 kcal/mol) provided the more stable conformer **I** (-18.2 kcal/mol). Complex **I** is less stable than **D** by 0.3 kcal/mol, but once the gold hydride moiety is removed and the free alkenes optimized, the endocyclic one is more stable by 1.6 kcal/mol.¹⁹ It is also worthy of note that the dissociation of **I** into the gold hydride **J** and the experimentally-observed alkene **8a** is exergonic by 2.2 kcal/mol (-20.4 kcal/mol). This is consistent with the fact that the formation of products **8** (Scheme 4b) is independent from that of the hydroarylation products (dissociative

Scheme 4. Mechanistic investigations.



pathway). Hydroarylation was modeled from **K** (-16.3 kcal/mol), which is simple conformer of **I** preorganized for

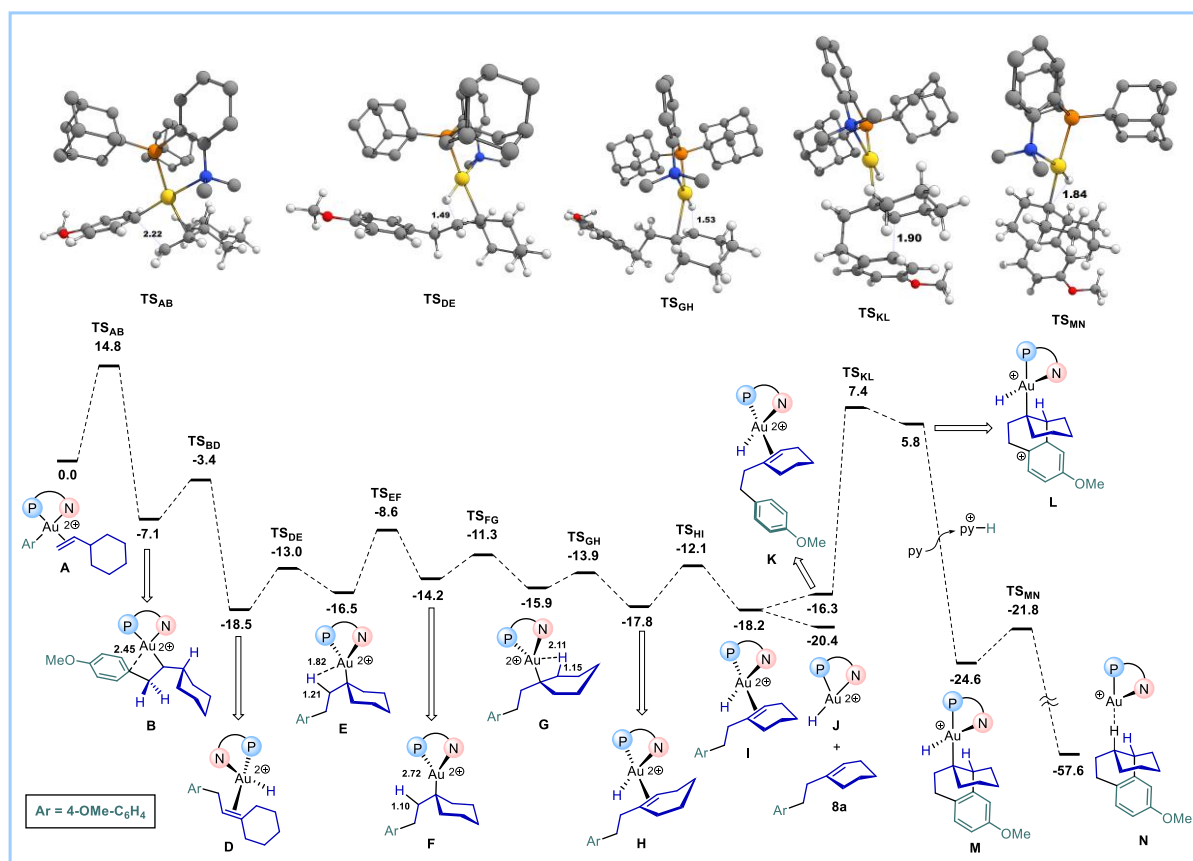
the *anti*-nucleophilic attack of the anisole fragment on the endocyclic alkene. A free energy of 23.7 kcal/mol must be overcome to reach **TS_{KL}** (25.9 kcal/mol from **D**). The Wheland intermediate **L** (5.8 kcal/mol) is, of course, obtained in a markedly endergonic fashion. Its deprotonation by pyridine would lead to **M** (-24.6 kcal/mol). Its reductive elimination through **TS_{MN}** (-21.8 kcal/mol) requires only 2.8 kcal/mol of free energy of activation. The experimentally observed *cis* product **N** (-57.6 kcal/mol) is finally obtained in a strongly exergonic manner. Various other modes of approach, as well as another Lewis acid ((P,N)Au(I)⁺), were tested, but these options proved more energetically demanding or ineffective.¹⁹

In conclusion, we have reported the first successful demonstration of the gold-catalyzed chain-walking under ligand-enabled Au(I)/Au(III) catalysis. Through the strategic utilization of chain walking, we have successfully developed gold-catalyzed annulation reaction of alkenes with iodoarenes. This methodology provided direct access to synthetically challenging tetrahydronaphthalene and octahydrophenanthrene derivatives with high diastereoselectivity. Given the realization of "chain-walking" in gold catalysis, along with the distinctive reactivities observed in contrast to other transition metals, we foresee significant opportunities emerging within the realm of organometallic catalysis.

Acknowledgments

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Figure 1. M11L/SDD+f(Au):6-311+G(d,p) free energy profile (ΔG_{298} , kcal/mol; some hydrogen atoms have been omitted for clarity; selected distances in Å).



References

- E. W. Werner, T.-S. Mei, A. J. Burckle, M. S. Sigman, *Science* 2012, 338, 1455–1458; b) T.-S. Mei, H. H. Patel, M. S. Sigman, *Nature* 2014, 508, 340–344; c) A. Vasseur, J. Bruffaerts, I. Marek, *Nat. Chem.* 2016, 8, 209–219; d) F. Juliá-Hernández, T. Moragas, J. Cornella, R. Martin, *Nature* 2017, 545, 84–88; e) H. Sommer, F. Juliá-Hernández, R. Martin, I. Marek, *ACS Cent. Sci.* 2018, 4, 153–165; f) R. K. Dhungana, R. R. Sapkota, D. Niroula, R. Giri, *Chem. Sci.* 2020, 11, 9757–9774; g) S. Ghosh, S. Patel, I. Chatterjee, *Chem. Commun.* 2021, 57, 11110–11130; h) D.-K. Wang, L. Li, Q. Xu, J. Zhang, H. Zheng, W.-T. Wei, *Org. Chem. Front.* 2021, 8, 7037–7049; i) D. Fiorito, S. Scaringi, C. Mazet, *Chem. Soc. Rev.* 2021, 50, 1391–1406; j) Y. Wang, Y. He, S. Zhu, *Acc. Chem. Res.* 2022, 55, 3519–3536.
- Y. He, Y. Cai, S. Zhu, *J. Am. Chem. Soc.* 2017, 139, 1061–1064; b) F. Zhou, J. Zhu, Y. Zhang, S. Zhu, *Angew. Chem. Int. Ed.* 2018, 57, 4058–4062; c) Y. Zhang, X. Xu, S. Zhu, *Nat. Commun.* 2019, 10, 1752–1760; d) Y. Zhang, B. Han, S. Zhu, *Angew. Chem. Int. Ed.* 2019, 58, 13860–13864; e) F. Zhou, Y. Zhang, X. Xu, S. Zhu, *Angew. Chem. Int. Ed.* 2019, 58, 1754–1758; f) J. Liu, H. Gong, S. Zhu, *Angew. Chem. Int. Ed.* 2021, 60, 4060–4064; g) Y. He, J. Ma, H. Song, Y. Zhang, Y. Liang, Y. Wang, S. Zhu, *Nat. Commun.* 2022, 13, 2471–2479.
 - Y.-W. Chen, Y. Liu, H.-Y. Lu, G.-Q. Lin, Z.-T. He, *Nat. Commun.* 2021, 12, 5626–5634.
 - T. C. Jankins, R. Martin-Montero, P. Cooper, R. Martin, K. M. Engle, *J. Am. Chem. Soc.* 2021, 143, 14981–14986; b) T. C. Jankins, W. C. Bell, Y. Zhang, Z.-Y. Qin, J. S. Chen, M. Gembicky, P. Liu, K. M. Engle, *Nat. Chem.* 2022, 14, 632–639.
 - T. Song, Y. Luo, K. Wang, B. Wang, Q. Yuan, W. Zhang, *ACS Catal.* 2023, 13, 4409–4420.
 - D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair, A. Sharma, *J. Am. Chem. Soc.* 2007, 129, 9592–9593; b) T. Kochi, T. Hamasaki, Y. Aoyama, J. Kawasaki, F. Kakiuchi, *J. Am. Chem. Soc.* 2012, 134, 16544–16547; c) R. Yu, S. Rajasekar, X. Fang, *Angew. Chem. Int. Ed.* 2020, 59, 21436–21441; d) X. Guo, Y. Wu, G. Li, J.-B. Xia, *ACS Catal.* 2020, 10, 12987–12995.
 - T. Kochi, K. Ichinose, M. Shigekane, T. Hamasaki, F. Kakiuchi, *Angew. Chem. Int. Ed.* 2019, 58, 5261–5265.
 - W. Wang, C. Ding, Y. Li, Z. Li, Y. Li, L. Peng, G. Yin, *Angew. Chem. Int. Ed.* 2019, 58, 4612–4616.
 - C. Han, Z. Fu, S. Guo, X. Fang, A. Lin, H. Yao, *ACS Catal.* 2019, 9, 4196–4202.
 - J.-P. Wang, S. Song, Y. Wu, P. Wang, *Nat. Commun.* 2022, 13, 5059–5068.
 - D. Zhu, Z. Jiao, Y. R. Chi, T. P. Gonçalves, K.-W. Huang, J. S. Zhou, *Angew. Chem. Int. Ed.* 2020, 59, 5341–5345.

- (12) a) P. Basnet, R. K. Dhungana, S. Thapa, B. Shrestha, S. KC, J. M. Sears, R. Giri, *J. Am. Chem. Soc.* 2018, 140, 7782–7786; b) R. K. Dhungana, S. KC, P. Basnet, V. Aryal, L. J. Chesley, R. Giri, *ACS Catal.* 2019, 9, 10887–10893.
- (13) a) Z. Chen, M. Brookhart, *Acc. Chem. Res.* 2018, 51, 1831–1839; b) Z. Guan, P. M. Cotts, E. F. McCord, S. J. McLain, *Science* 1999, 283, 2059–2062; c) T. Okada, S. Park, D. Takeuchi, K. Osakada, *Angew. Chem. Int. Ed.* 2007, 46, 6141–6143; d) T. Okada, D. Takeuchi, A. Shishido, T. Ikeda, K. Osakada, *J. Am. Chem. Soc.* 2009, 131, 10852–10853; e) D. Takeuchi, *J. Am. Chem. Soc.* 2011, 133, 11106–11109.
- (14) Reviews: a) P. Garcia, M. Malacria, C. Aubert, V. Gandon, L. Fensterbank, *ChemCatChem.* 2010, 2, 493–497; b) H. A. Wegner, M. Auzias, *Angew. Chem. Int. Ed.* 2011, 50, 8236–8247; c) M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Chem. – Eur. J.* 2011, 17, 8248–8262; d) J. Miró, C. del Pozo, *Chem. Rev.* 2016, 116, 11924–11966; e) M. N. Hopkinson, A. Tlahuext-Aca, F. Glorius, *Acc. Chem. Res.* 2016, 49, 2261–2272; f) M. O. Akram, S. Banerjee, S. S. Saswade, V. Bedi, N. T. Patil, *Chem. Commun.* 2018, 54, 11069–11083; g) A. Nijamudheen, A. Datta, *Chem. – Eur. J.* 2020, 26, 1442–1487; h) S. Banerjee, V. W. Bhojare, N. T. Patil, *Chem. Commun.* 2020, 56, 2677–2690; i) B. Huang, M. Hu, F. D. Toste, *Trends Chem.* 2020, 2, 707–720; j) C. Fricke, W. B. Reid, F. A. Schoenebeck, *Eur. J. Org. Chem.* 2020, 7119–7130; k) S. Witzel, A. S. K. Hashmi, J. Xie, *Chem. Rev.* 2021, 121, 8868–8925; l) Z. Zheng, X. Ma, X. Cheng, K. Zhao, K. Gutman, T. Li, L. Zhang, *Chem. Rev.* 2021, 121, 8979–9038; m) P. Font, X. Ribas, *Eur. J. Inorg. Chem.* 2021, 2556–2569; n) V. W. Bhojare, A. G. Tathe, A. Das, C. C. Chintawar, N. T. Patil, *Chem. Soc. Rev.* 2021, 50, 10422–10450; o) S. B. Ambegave, N. T. Patil, *Synlett* 2023, 34, 698–708.
- (15) a) G. Klatt, R. Xu, M. Pernpointner, L. Molinari, T. Q. Hung, F. Rominger, A. S. K. Hashmi, H. Köppel, *Chem. – Eur. J.* 2013, 19, 3954–3961; b) M. Joost, A. Amgoune, D. Bourissou, *Angew. Chem. Int. Ed.* 2015, 54, 15022–15045.
- (16) a) N. P. Mankad, F. D. Toste, *Chem. Sci.* 2012, 3, 72–76; b) D.-A. Roşca, D. A. Smith, D. L. Hughes, M. A. Bochmann, *Angew. Chem. Int. Ed.* 2012, 51, 10643–10646; c) M. Joost, L. Estevez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, *J. Am. Chem. Soc.* 2014, 136, 10373–10382; d) E. Langseth, A. Nova, E. A. Tråseth, F. Rise, S. Øien, R. H. Heyn, M. A. Tilset, *J. Am. Chem. Soc.* 2014, 136, 10104–10115; e) F. Rekhroukh, R. Brousses, A. Amgoune, D. Bourissou, *Angew. Chem. Int. Ed.* 2015, 54, 1266–1269; f) F. Rekhroukh, L. Estevez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, *J. Am. Chem. Soc.* 2016, 138, 11920–11929; g) M. C. Reis, C. S. López, E. Kraka, D. Cremer, O. N. Faza, *Inorg. Chem.* 2016, 55, 8636–8645; h) F. Rekhroukh, C. Blons, L. Estévez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, *Chem. Sci.* 2017, 8, 4539–4545; i) R. Kumar, J.-P. Krieger, E. Gómez-Bengoia, T. Fox, A. Linden, C. Nevado, *Angew. Chem. Int. Ed.* 2017, 56, 12862–12865; j) J. Serra, P. Font, E. D. Sosa Carrizo, S. Mallet-Ladeira, S. Massou, T. Parella, K. Miqueu, A. Amgoune, X. Ribas, D. Bourissou, *Chem. Sci.* 2018, 9, 3932–3940; k) M. S. M. Holmsen, C. Blons, A. Amgoune, M. Regnacq, D. Lesage, E. D. Sosa Carrizo, P. Lavedan, Y. Gimbert, K. Miqueu, D. Bourissou, *J. Am. Chem. Soc.* 2022, 144, 22722–22733; l) J. A. Cadge, P. J. Gates, J. F. Bower, C. A. Russell, *J. Am. Chem. Soc.* 2022, 144, 19719–19725.
- (17) V. W. Bhojare, E. D. Sosa Carrizo, C. C. Chintawar, V. Gandon, N. T. Patil, *J. Am. Chem. Soc.* 2023, 145, 8810–8816.
- (18) W. Wang, M. Ding, C.-G. Zhao, S. Chen, C. Zhu, J. Han, W. Li, J. Xie, *Angew. Chem. Int. Ed.* 2023, e202304019.
- (19) For details, see the Supporting Information.