A C−H Insertion Approach to Functionalized Cyclopentenones

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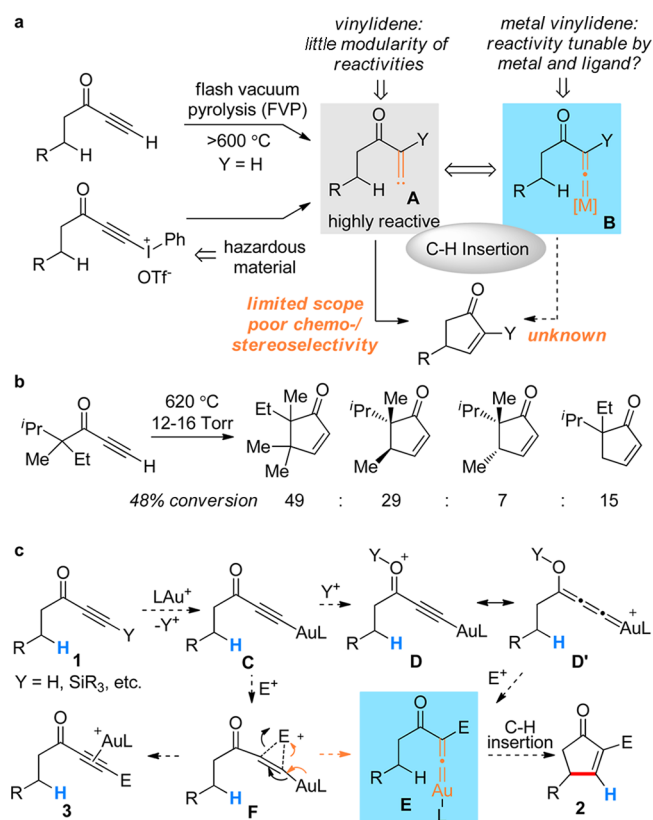
Ⓢ *Supporting Information*

ABSTRACT: Cyclopentenones are synthetically versatile structures, and their straightforward construction from alkynone substrates by employing synthetically stream-lining C−H insertion is conceptually appealing and of high synthetic potential. But, its implementation is very limited. Herein we report a Au-catalyzed version, which affords 2-bromocyclopent-2-en-1-ones with a broad scope and synthetically desirable diastereoselectivities. The proposed key intermediate capable of the observed insertion into unactivated C−H bonds is a fully functionalized gold vinylidene, which is generated via a novel intermolecular strategy. This flexible access of likely gold vinylidenes opens various opportunities to explore their versatile reactivities.

Ⓒyclopentenones are versatile and indispensable structural motifs in the synthesis of functional molecules. Its straightforward construction via alkynone cyclization employs a synthetically streamlining C−H insertion by a reactive alkenylidene intermediate[1] (i.e., **A**, Scheme 1a). Despite the approach being conceptually appealing and of high synthetic potential, its reported implementations are limited to flash vacuum pyrolysis (FVP, >600 °C)[2] and in one study the use of hazardous α-ketoethynyl(phenyl)iodonium salts.[3] Both approaches, however, have no additional control of the reactivities of alkenylidene intermediates. Consequently, these reactions have limited scope and often display poor regioselectivity and low diastereoselectivity (as exemplified in Scheme 1b).[2a]

An enduring and highly rewarding practice of modulating the reactivities of reactive species and achieving their chemo-/regio-/stereoselective transformations is the employment of transition-metal complexes. As such, metal vinylidene/alkenylidene complexes with various transition metals, many stable and isolable, have been employed as versatile and often catalytic intermediates en route to the development of various valuable synthetic methods.[4] Despite extensively researched, they seldom undergo insertions into C−H bonds.[5] Consequently, the metal-catalyzed formation of cyclopentenones via C−H insertion by metal vinylidene species has not been realized.

Recent developments in homogeneous Au catalysis have revealed that in situ-generated gold vinylidenes are uniquely reactive and do undergo insertions into C−H bonds.[6] For the cases with DFT support,[6a,c,e] their generations are, however, confined to conformationally rigid (2-ethynylphenyl)alkynes, which are of necessity due to a limiting intramolecular generation

Scheme 1. C−H Insertion Approaches to Functionalized Cyclopentenones[a]

[a](a) Formation of cyclopentenones via C−H insertions of vinylidene intermediates in the absence of corresponding metal-mediated or -catalyzed process. (b) Poor selectivity in one example of α-alkynone cyclization. (c) Design for intermolecular access to fully functionalized gold vinylidenes from ynones and their C−H insertion reactions.

mechanism. As such, there is a need of developing flexible intermolecular generation of versatile gold vinylidenes.

To develop a novel intermolecular strategy of generating gold vinylidenes and especially so in the context of forming the synthetically highly valuable cyclopentenones via richly function-alized metal vinylidene **B**, it is envisioned that, as shown in Scheme 1c, the α-alkynone **1** could first be converted to the alkynylgold complex **C** when treated with a cationic Au complex.

Table 1. Initial Reaction Discovery and Condition Optimization

entry	Y	AgX	"Br+"	temp (°C)/ time (h)	conv (%)	yield[a] (%)	
						2a/2a'	1a-Br
1	H	AgNTf$_2$	NBS	60/12	88	5 (–)	<2
2	H	AgOTf	NBS	60/4	100	49 (>12/1)	10
3	H	AgSbF$_6$	NBS	rt/18	100	61 (>17/1)	<2
4	H	AgSbF$_6$ (5 mol%)	NBS	rt/18	84	24	<2
5	H	AgSbF$_6$ (20 mol%)	NBS	rt/5	100	48	<2
6	H	AgSbF$_6$	NBP	rt/18	100	47 (>32/1)	<2
7	H	AgSbF$_6$	NBA	rt/7	100	86 (>20/1)	12
8	TMS	AgSbF$_6$	NBA	rt/7	100	95 (>40/1)	<2
9	TES	AgSbF$_6$	NBA	rt/48	19	16 (5/1)	<2
10	Br	AgSbF$_6$	–	rt/48	22	0	78
11	TMS	AgSbF$_6$[b]	NBA	rt/7	62	0	60
12[c]	TMS	AgSbF$_6$	NBA	rt/7	51	20 (>20/1)	12
13[d]	TMS	AgSbF$_6$	NBA	rt/3.5	100	87 (>20/1)	<2
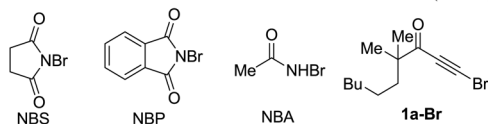
[a]Reactions run in vial. Yields estimated by ^{1}H NMR using diethyl phthalate as internal reference. [b]No Au used. [c]4 Å MS added. [d]H$_2$O (4 equiv relative to 1a) added.

The byproduct of this process, i.e., Y$^+$, might then activate the electron-withdrawing acyl group of **C**, thereby further polarizing its C–C triple bond. As such, the C(sp) β to Au might possess significant nucleophilicity, as reflected in the allenylidene mesoisomer **D'**[7] and could react with an electrophile to render a fully functionalized gold vinylidene **E**. Intramolecular C–H insertions by this likely reactive species would afford the functionalized cyclopentenone **2**. Alternatively, **C** might react with electrophiles to arrive via **F**, at **E** or the Au-coordinated electrophile-substituted alkynone **3**.

We set out to probe the validity of our design by using the alkynone **1a-H** (Y = H) as the substrate and NBS as the electrophilic source (Table 1). **1a-H** bears an α'-quaternary carbon center, which should facilitate the desired intramolecular C–H insertion due to the Thorpe–Ingold effect. While only trace amount of the desired products **2a**/**2a'** were detected in the presence of Au catalysts with phosphine ligands such as Ph$_3$P, BrettPhos, and Mor-DalPhos at 80 °C, much to our delight, it was formed in an encouraging 5% yield along with trace amount of the bromoalkyne **1a-Br** when the N-heterocyclic carbene IPr

was used as the metal ligand (entry 1). The counteranion is important, and among the ones examined (entries 1–3), SbF$_6$$^-$ is the most effective, and the cyclopentenone products were formed in 61% yield at room temperature (entry 3). We then varied the amount of AgSbF$_6$ (entries 4 and 5), and it appeared that 2 equiv of it to IPrAuCl is ideal. Different brominating reagents were then screened. In comparison to NBS, the more reactive NBP (N-bromophthalimide) led to a diminished yield (entry 6), while 86% yield was achieved by using N-bromoacetamide (NBA), a less reactive brominating reagent (entry 7). With **1a-TMS** (Y = TMS) as substrate, the reaction was even more efficient, affording **2a** in an outstanding 95% yield without noticeable impact on the reaction rate (entry 8). On the other hand, sterically more demanding TES greatly retarded the reaction, resulting in a low conversion in 48 h (entries 9). Notably, the bromoalkynone **1a-Br** did not participate in the reaction (entry 10), which rules out its potential role as a reaction intermediate, and the silver salt alone is not the catalyst (entry 11). We also observed residual H$_2$O from undried vial is beneficial to the reaction. In its absence (entry 12), the reaction was much less efficient, and the addition of H$_2$O (4 equiv) led to an accelerated reaction, despite a slightly lower yield (entry 13). Finally, DCM is an equally accommodating solvent, and the α-bromocyclopentenone product was isolated in 95% yield. In all the cases the reaction is highly regioselective, as the methylene C–H bonds are preferred over the methyl ones by a ratio of >20/1, consistent with IPrAu modulating the reactivity of reactive vinylidene.

Notably, cyclopentenones are in general of exceptional synthetic utility, and the products accessible via this streamlining C–H insertion strategy possess additional α-bromination and hence are of even higher synthetic value. Synthetic applications of these compounds include, to name a few, enantioselective synthesis of aplyviolene,[8] a concise route to bioactive hypnophilin,[9] and the synthesis of marine prostanoid analogues.[10]

This rapid access to highly versatile α-bromocyclopentenone prompted us to explore extensively the reaction scope, which is shown in Table 2. Similar to **1a-TMS**, TMS-terminated ynones **1b**–**1d** bearing α'-quaternary C centers all undergo the C–H insertive cyclization smoothly, regardless of the increased steric congestion in entries 1 and 3 and a deactivated benzylic C–H bond in entry 2. In the latter case, side products derived from methyl C–H insertion and phenyl participation are observed.[11] The reaction is not limited to α-alkynones bearing α-quaternary C's. The unbranched TMS-terminated ynone **1e** (entry 4) worked smoothly, affording **2e** in a good 74% yield. Functional groups such as OTs, OTBDPS, and Br can be tolerated (entries 5–7). However, we observed that the closer an inductively electron-withdrawing group is to the inserted C–H bond, the more sluggish the reaction is. For example, the reaction of **1f** with a γ'-OTBDPS group led to 51% yield with a higher catalyst loading and in longer time (entry 5). If the siloxyl group is replaced with a more inductive OTs, no desired C–H insertion product was detected. This phenomenon suggests an asynchronous C–H insertion step where partial positive charge is developed at the carbon center in the transition state.

The diastereoselectivity and regioselectivity of this reaction were then interrogated. While the reaction of the α'-methyl ynone **1i** displays synthetically useful preference (dr = 4/1) toward the trans-isomer (entry 8), replacing its n-butyl group with an isopropyl group in **1j**, as expected, substantially improved the diastereoselectivity (entry 9). On the other hand, a

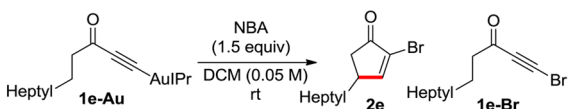**Table 2. Scope of Au-Catalyzed Cyclopentenone Synthesis[a]**
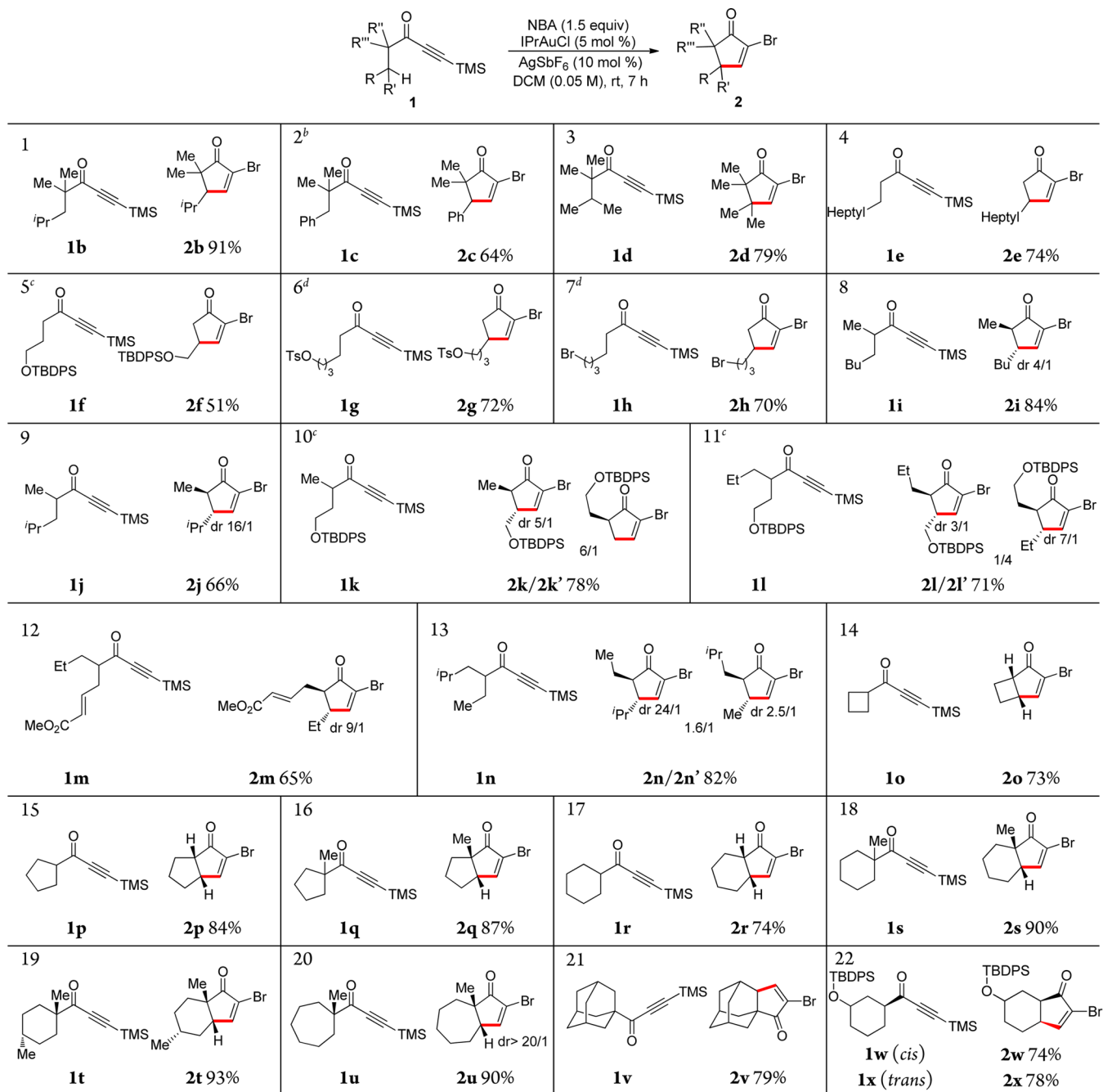
TBDPSOCH$_2$ group in **1k** led to significant amount of insertion into methyl C−H bonds (entry 10), which is consistent with the retarding effect of electron-withdrawing groups, while the diastereoselectivity of the major product **2k** remained serviceable and the combined yield is good. When the methyl group of **1k** is replaced by a propyl group (**1l**), the regioselectivity now favors insertion into the nonfunctionalized alkyl chain by a ratio of 4/1, highlighting the useful control of regiochemistry by subtle electronic difference (entry 11). In the same vein, the C−H bonds at the allylic position of an α,β-unsaturated ester **1m** is largely deactivated for the intended insertion, and only the insertion into the n-propyl en route to **2m** was observed (entry

12). Finally, the ynone **1n** with two electronically similar but sterically different alkyl chains was subjected to the reaction conditions. The reaction is highly efficient, but with a regioselectivity of 1.5/1 favoring insertion into the sterically more hindered methylene group (entry 13). This surprising outcome reflects the insensitive nature of the gold vinylidene toward steric hindrance due to its linear structure, and the slight preference for **2n** is consistent with that electronically an α-isopropyl group is better accommodating the development of partial positive charge than an α-methyl group.

The synthetic utility of this Au catalysis is further demonstrated by insertions into carbocycles of varying sizes/

Table 3. Mechanistic Studies

entry	additive	time	yield[a] (%)	
			2e	**1e-Br**
1	none	36 h	0	70
2	AgSbF$_6$ (0.05 equiv)	1 h	trace	dec.
3	IPrAuNTf$_2$ (0.05 equiv)	1 h	trace	dec.
4	AgSbF$_6$ (1.5 equiv)	1 h	55	dec.
5	TMSOTf (1.5 equiv)	1 h	16	dec.
6	NBS instead of NBA	50 min	0	85

[a]Reactions run in vial. Yields estimated by ^{1}H NMR using diethyl phthalate as internal reference.

types (entries 14−22) including a strained cyclobutane (entry 14). These reactions are highly efficient, with yield up to an outstanding 93% and, moreover, display excellent diastereo-selectivities of *cis*-ring fusion in the bicyclic products including the cyclohexane-fused ones **2r**−**2t** and the cycloheptane-fused one **2u**. In the reactions of cyclopentane and cyclohexane substrates, the Thorpe−Ingold effect does lead to improved yields, with the latter more significant (comparing entries 17 and 18). This reaction also worked with 1-adamantyl ketone **1v**, and the adamantane-fused 2-bromocyclopentenone **2v** is isolated in a good 79% yield. Using dithiane Umpolung strategy, TBDPSO-substituted cyclohexyl ynone diastereomers **1w** and **1x** were facilely synthesized in four steps from cyclohexenone and ((1,3-dithian-2-yl)ethynyl)trimethylsilane and separated pure. Due to the steric and electronic deactivating effect of TBDPSO group, high regioselectivities were achieved in both cases, and synthetically versatile **2w** and **2x** were isolated in good yields.

To offer mechanistic support to our initial design, we synthesized the alkynylgold complex **1e-Au** and treated it with NBA (Table 3). The consumption of **1e-Au** took 36 h. To our surprise, the desired product **2e** was not detected. Instead, the bromoalkynone **1e-Br** was isolated in 70% yield. As bromoalkynones are not the reaction intermediate en route to the 2-bromocyclopentenones (see Table 1, entry 10), this outcome suggests a critical role of the in situ-generated TMS$^+$/H$^+$ and/or excess AgSbF$_6$. Indeed, the desired vinylidene insertion could be resurrected when AgSbF$_6$ (entries 2 and 4) or TMSOTf (entry 5) was added, albeit with lower yields. These results confirmed the intermediacy of **1e-Au**. In all the cases, **1e-Br** was formed immediately but subsequently decomposed during the reaction. It is plausible that these acidic additives might play the role of activating NBA to make its bromine more electrophilic. To test this hypothesis, we replaced NBA with more reactive NBS. **1e-Au** was consumed in only 50 min by NBS (entry 6), but to our surprise, only **1e-Br** was formed. This result does not support the role of the acidic species in activating NBA but is consistent with the mechanism outlined in Scheme 1c, where the gold ynone intermediate **C** is instead activated by acidic Y$^+$ and undergoes the formation of gold vinylidene **E** via the allenylidene species **D′**.[7] It is noteworthy that bromoalkynes are formed in the absence of the carbonyl group.

In summary, we have developed the first metal-catalyzed alkynone cyclization, which enables facile access to synthetically highly versatile functionalized cyclopentenones. While non-catalytic reactions involving reactive vinylidene intermediates, typically lead to poor selectivities, the Au catalysis developed here permits the use of readily available substrates at ambient temperature and most important, owing to the modulation by Au, enables C−H insertion with good regio- and diastereo-selectivities. In addition, this work demonstrates an unprecedented intermolecular strategy to access functionalized gold vinylidenes, which enables valuable flexibility in exploring their versatile synthetic utility.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04297.

Experimental details and data (PDF)

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164.
(2) (a) Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1979**, *62*, 852. (b) Karpf, M.; Huguet, J.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 13.
(3) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93.
(4) *Metal vinylidenes and allenylidenes in catalysis from reactivity to applications in synthesis*; Bruneau, C., Dixneuf, P. H., Eds.; Wiley-VCH: Weinheim, 2008.
(5) (a) Bajracharya, G. B.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6204. (b) Odedra, A.; Datta, S.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 3289.
(6) (a) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31. (b) Hashmi, A. S. K.; Braun, I.; Noesel, P.; Schaedlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456. (c) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2593. (d) Vachhani, D. D.; Galli, M.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V. *Chem. Commun.* **2013**, *49*, 7171. (e) Hansmann, M. M.; Tsupova, S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Chem. - Eur. J.* **2014**, *20*, 2215. (f) Morán-Poladura, P.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 3052. (g) McGee, P.; Bellavance, G.; Korobkov, I.; Tarasewicz, A.; Barriault, L. *Chem. - Eur. J.* **2015**, *21*, 9662. (h) Bucher, J.; Wurm, T.; Nalivela, K. S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 3854.
(7) (a) Hansmann, M. M.; Rominger, F.; Hashmi, A. S. K. *Chem. Sci.* **2013**, *4*, 1552. (b) Xiao, X.-S.; Kwong, W.-L.; Guan, X.; Yang, C.; Lu, W.; Che, C.-M. *Chem. - Eur. J.* **2013**, *19*, 9457. (c) Jin, L.; Melaimi, M.; Kostenko, A.; Karni, M.; Apeloig, Y.; Moore, C. E.; Rheingold, A. L.; Bertrand, G. *Chem. Sci.* **2016**, *7*, 150.
(8) Schnermann, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **2011**, *133*, 16425.
(9) Geng, F.; Liu, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 71.
(10) Kuhn, C.; Roulland, E.; Madelmont, J.-C.; Monneret, C.; Florent, J.-C. *Org. Biomol. Chem.* **2004**, *2*, 2028.
(11) Side products are

2c′, 8%   **3c**, 7%