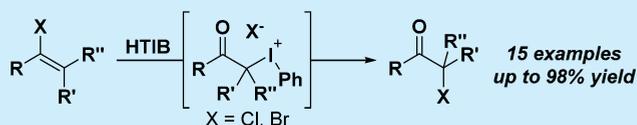# Iodine(III)-Mediated Oxidative Hydrolysis of Haloalkenes: Access to α-Halo Ketones by a Release-and-Catch Mechanism

Antoine Jobin-Des Lauriers and Claude Y. Legault*

University of Sherbrooke, Department of Chemistry, Centre in Green Chemistry and Catalysis, 2500 boul. de l'Université, Sherbrooke, Québec J1K 2R1, Canada

Ⓢ *Supporting Information*

ABSTRACT: An unprecedented iodine(III)-mediated oxidative transposition of vinyl halides has been accomplished. The products obtained, α-halo ketones, are useful and polyvalent synthetic precursors. There are only a handful of reported examples of the direct conversion of vinyl halides to their corresponding α-halo carbonyl compounds. Insights into the mechanism and demonstration that this synthetic transformation can be done under enantioselective conditions are reported.

Although hypervalent iodine reagents have been known for over a century, they have recently become a subject of growing and keen interest in the field of chemistry.[1] In addition to being mild, selective, eco-friendly, and versatile oxidants, iodine(III) and iodine(V) reagents have also proven their utility in performing synthetically relevant transformations, such as phenolic dearomatizations[2] and various other oxidative rearrangements.[3] They can also act as safer alternatives to some toxic metal-based oxidants, such as thallium.[4] Lately, there have been numerous efforts in the development of stereoselective methods involving these reagents.[5]

The iodine(III)-mediated synthesis of functionalized ketone derivatives has been a particularly active area of research.[6] This is not surprising considering the ubiquitous nature of α-functionalized ketones in natural and synthetic compounds. One particularly useful approach exploits iodine(III) chemistry to introduce by oxidation a leaving group at the α position of the carbonyl (Scheme 1a). If performed under enantioselective

Scheme 1. Concept of the Described Research
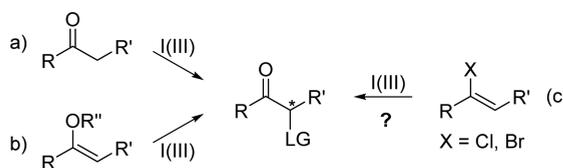
conditions, the resulting products are versatile chiral precursors for stereoselective synthesis. In this context, our group has been interested in the synthesis of chiral nonracemic α-tosyloxy ketone derivatives. For more than 15 years, the published methods involved the direct α-tosyloxylation of ketones.[7] Recently, we have raised the issue that the probable mechanism involved for the direct α-tosyloxylation of ketones could prevent achievement of high enantioselectivities.[8] In an effort to solve this issue, we have developed reaction conditions that have given access to the desired α-tosyloxy ketones from their

corresponding enol esters (Scheme 1b, R″ = Ac), with unprecedented levels of enantioselectivities (up to 90% *ee*).[9]

We envisioned that other vinylic substrates having the same oxidation state as enol derivatives, such as vinyl halides, could thus serve as α-substituted ketone precursors (Scheme 1c). Only scarce examples are found in the literature for the direct conversion of vinyl halides to their corresponding α-halo ketone derivatives.[10] In analogy to α-tosyloxy ketones, the α-halo ketones families have the same versality and are common and useful building blocks in synthetic chemistry.[11]

Accessing these products from the vinyl halides family is particularly interesting in this regard, due to the numerous synthetic methods to access them from nonketonic precursors.[12] We report herein the oxidation of vinyl halides to their corresponding α-halo ketones in high yields and mild conditions.

To evaluate the reactivity of the described compound family, we elected to use vinyl halides **1a** and **1b**, derived from octanophenone, for the low volatilities of the substrates and final products. For the sake of simplicity, these substrates were obtained directly from the ketone.[13] The results of the optimization are described in Table 1. The reaction of **1a** with [hydroxy(tosyloxy)iodo]benzene (HTIB) did not result in the formation of the α-tosyloxy ketone product, but instead its chloro analog (**2a**). The formation of acid derivatives **3** in small amounts was observed as a consequence of 1,2-aryl migration. Isolated yields of **3** compounds could not be obtained due to their partial and continuous hydrolysis over the course of the purification by flash chromatography on silica gel.

The effect of adding TsOH·H₂O in increasing amounts was studied to determine if this additive could accelerate the reaction rate, as it was previously observed for the reaction of HTIB with enol esters.[14] It was found to furnish a great acceleration effect, while not affecting the relative **2a/3**
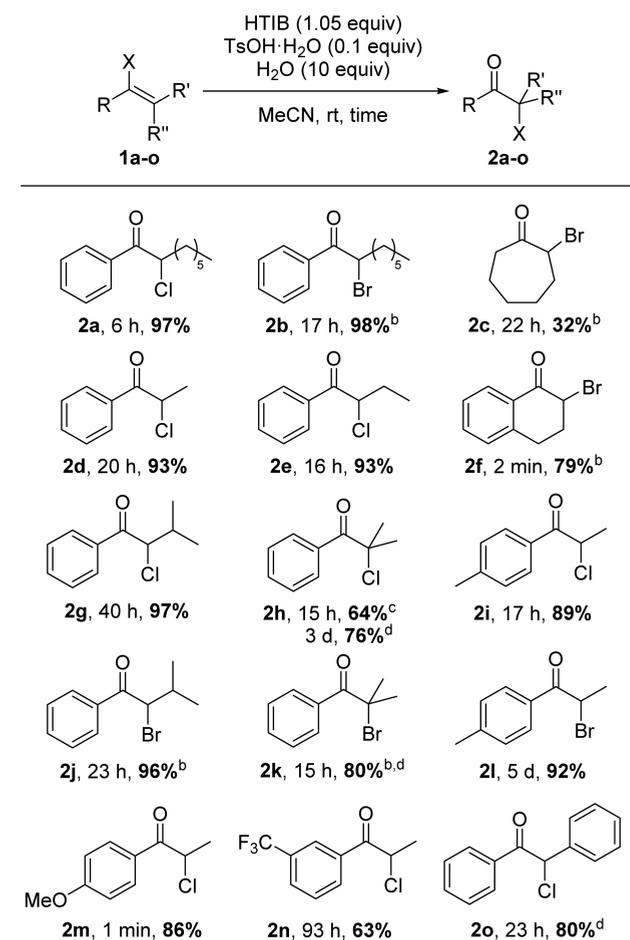
Table 1. Conditions Screening[a]

1a (X = Cl)
1b (X = Br)

2a (X = Cl)
2b (X = Br)

3
R = OTs, Cl, OH

entry	TsOH (equiv)	solvent	time (h)	2 [%][b]	3 [%][c]
1	0	MeCN	20	69	15
2	0.1	MeCN	5	77	18
3	0.5	MeCN	2	79	21
4	1	MeCN	1.5	80	20
5	0.1	MeCN[d]	6	97	<2
6	0.1	MeCN/H$_2$O (1:1)	24	76	<2
7	0.1	H$_2$O	72	29	<2
8	0.1	CH$_2$Cl$_2$	48	68	20
9	0.1	CH$_2$Cl$_2$[d]	26	70	30
10	0.1	EtOAc	72	46	<2
11	0.1	THF	1	53	<2
12[e]	0.1	MeCN[d]	17	86	<2
13[e]	0.1	MeCN	17	98	<2

[a]Unless otherwise stated, 1a was used. [b]Isolated yield. [c]Yield determined by ^{1}H NMR of the crude mixture, with respect to isolated 2. [d]10 equiv of water were added to the reaction. [e]Reaction performed with 1b.

formation ratio (entries 2−4). Since the concentration of TsOH increases as HTIB is reduced during the reaction process, a substoichiometric loading (0.1 equiv) of TsOH is sufficient to achieve noticeable overall acceleration, and was used for the remainder of the optimization. As hydrolysis is most probably involved in the reaction process, the effect of water was next evaluated. Addition of 10 equiv of water resulted in no acceleration, but in a very clean conversion of 1a to 2a, with no detectable aryl migration products 3 (entry 5). Attempts to perform the reaction in either equivolumic MeCN/water solution or directly in water resulted in lower yields of 2a, but no observable formation of phenyl migration products (entries 6−7). Other solvents (entries 8−11) were tested, but only resulted in lower yields and side products formation. The addition of 10 equiv of water in dichloromethane did not prevent the formation of migration products 3. The optimized conditions were evaluated on vinyl bromide 1b; a lower yield and no migration products were observed (entry 12). The presence of the α-hydroxy ketone in the crude mixture suggested susceptibility of 2b toward hydrolysis. The reaction was thus was performed without the addition of water; the α-bromo product 2b was obtained in essentially quantitative yield, with no noticeable migration products (entry 13).

With these optimized conditions in hand, the scope of this new transformation was investigated with various vinyl chlorides and bromides. The results are summarized in Scheme 2. The transformation is efficient on styrene analogs (R = aromatic), with excellent yields in most cases. It is important to point out that it does however proceed with some success on fully aliphatic substituted vinyl bromide 1c, affording product 2c with 32% yield. Conversion of 1c was complete, with the formation of numerous unidentified side products.

The method supports variation on the other portion of the styrene derivatives (R′, R″). For example, vinyl chloride and bromide 1g and 1j, respectively, were converted in almost quantitative yields to their respective α-halo ketone products.

Scheme 2. Reaction Scope[a]

1a-o

2a-o

2a, 6 h, 97%

2b, 17 h, 98%[b]

2c, 22 h, 32%[b]

2d, 20 h, 93%

2e, 16 h, 93%

2f, 2 min, 79%[b]

2g, 40 h, 97%

2h, 15 h, 64%[c]
3 d, 76%[d]

2i, 17 h, 89%

2j, 23 h, 96%[b]

2k, 15 h, 80%[b,d]

2l, 5 d, 92%

2m, 1 min, 86%

2n, 93 h, 63%

2o, 23 h, 80%[d]

[a]Isolated yields reported. [b]No water was added in the reaction. [c]Reaction performed at 55 °C. [d]Reaction performed at 40 °C.

The reaction can even proceed on tetrasubstituted vinyl halides (1h and 1k), although higher reaction temperatures (40−55 °C) are required to obtain complete conversion. Cyclic vinyl bromide 1f afforded the desired product 2f in a very fast reaction. In the last three cases, the lower yield is attributed to partial formation of the enone products. These results are in stark contrast with the behavior observed for the corresponding enol ester analogs, which afforded mainly the formation of the corresponding enones in low yield.[13,14] The electronic properties of the aromatic group of the styrene derivatives greatly affect the reactivity. Vinyl halide 1m, bearing a p-methoxy phenyl group, is converted almost instantly to product 2m. The lower yield is attributed to numerous unidentified side products, but aryl migration products 3 are observed in higher quantities in the crude mixture. In contrast, almost 4 days of reaction are required to achieve complete conversion of substrate 1n, bearing a p-trifluoromethyl phenyl group. The described methodology demonstrates a larger scope than the known methods to directly convert vinyl halides to α-halo ketones.

During the optimization process, the observation of the aryl migration products 3 prompted the investigation of the reaction mechanism. These products point toward a potential internal transposition of the halogen atom in the reaction process. To assess the feasibility of the latter versus an external halide attack manifold, a scrambling experiment was performed.

An equimolar mixture of substrates **1d** and **1j** was subjected to the optimized reaction conditions. The outcome is presented in Scheme 3.

Scheme 3. Scrambling Experiment
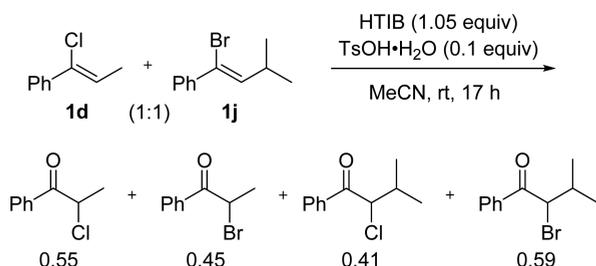
Starting from an equimolar mixture of vinyl halides **1d** and **1j**, the four possible α-halo ketone products were observed in almost equimolar quantities. The slight variance in ratio could be explained by either the different rates of conversion of **1d** and **1j** or competing mechanisms. It is clear however that the main reaction pathway does not consist of an internal halide migration, but an external halide attack. Addition of 10 equiv of water did not change noticeably the scrambling outcome. The possibility of the formation of the α-tosyloxy ketone product and subsequent S_N2 by a halide was infirmed; a displacement reaction with HCl in similar reaction conditions was found to be very slow (35% conversion in 36 h) in a control experiment.[13] Additionally, the α-tosyloxy ketone products were not observed in the crude reaction mixtures, even if the reactions were stopped prior to completion. With these experimental clues in hand, we proposed at the moment the mechanism illustrated in Scheme 4.

Scheme 4. Proposed Mechanism
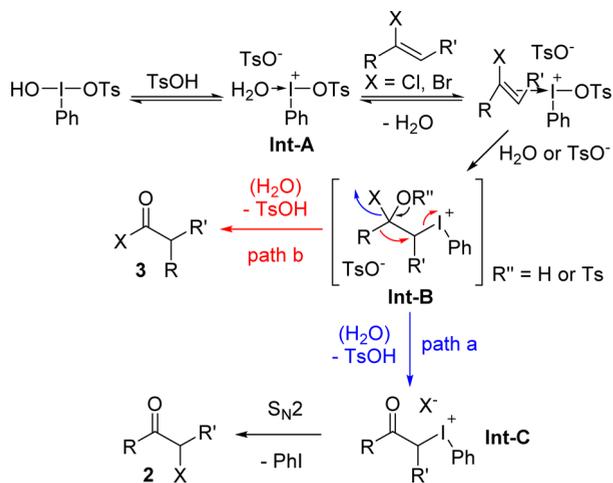
As observed for the enol esters, the acceleration in the presence of TsOH is attributed to the formation of the phenyl tosyloxy iodonium intermediate **Int-A**, which is suggested to be the reactive iodine(III) species. Association of the vinyl halide and attack of a nucleophile (TsO⁻ or H_2O) lead to the formation of intermediate iodonium **Int-B**. At this point, depending on the rate of halide expulsion and migratory aptitude of the R group, there can be competing internal aryl migration through a semipinacolic displacement of PhI. In the case of vinyl chloride substrates, addition of water is necessary to accelerate expulsion of the chloride anion, through better solvation, and prevent formation of products **3**. In the case of vinyl bromides, the bromide anion is a better leaving group, and the competing aryl migration is not observed. No α-tosyloxy ketone is observed as the conjugate base of the strongest acid (HCl and HBr vs TsOH) will be the counterion of the iodonium intermediate **Int-C** and lead, by S_N2 substitution, to the final product. We refer to this pathway as a "release-and-catch" mechanism.

This unusual mechanism would have strong implications on the stereochemical aspects of this reaction. We thus tested preliminary enantioselective conditions to determine if this transformation would only furnish racemic products. The result is illustrated in Scheme 5.

Scheme 5. Enantioselective Conditions
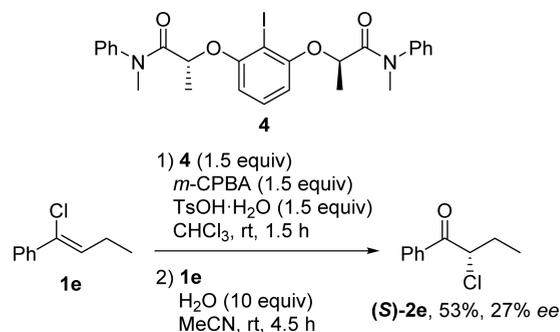
While the enantioselectivity observed is modest, the fact that the product is not racemic is very promising for the development of an enantioselective variant of this new transformation. The sense of induction was found to be the same as that obtained with enol esters using chiral iodoarene **4**,[9] suggesting a similar reaction process. To the best of our knowledge, this is the first example of an enantioselective conversion of a prochiral vinyl halide to a corresponding chiral nonracemic α-halo ketone.

In summary, this new iodine(III)-mediated transformation shows high potential to serve as a very useful synthetic tool. This methodology will be of great interest for the synthetic community considering the variety of methods to synthesize vinyl halides and the utility of α-halo ketone derivatives. The results described herein also raise numerous interesting questions for the field of hypervalent iodine chemistry. It is clear from the control experiments and the results obtained under enantioselective conditions that several aspects of the mechanism will need to be investigated in order to fully exploit this highly promising process. Joint computational/experimental investigations are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03345.

Experimental procedures and NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: claude.legault@usherbrooke.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Zhdankin, V. V. *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*; Wiley: Chichester, U.K., 2013. (b) Tohma, H.; Kita, Y. In *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer: Berlin, 2003; p 209. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Moriarty, R. M.; Prakash, O. *Org. React.* **2001**, *57*, 327. (e) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997.

(2) (a) Bosset, C.; Coffinier, R.; Peixoto, P. A.; El Assal, M.; Miqueu, K.; Sotiropoulos, J.-M.; Pouységu, L.; Quideau, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9860. (b) Volp, K.; Harned, A. M. *Chem. Commun.* **2013**, *49*, 3001. (c) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 9215. (d) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175. (e) Uyanik, M.; Yasui, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841. (f) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (g) Boppisetti, J. K.; Birman, V. B. *Org. Lett.* **2009**, *11*, 1221. (h) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787.

(3) (a) Singh, F. V.; Wirth, T. *Chem. - Asian J.* **2014**, *9*, 950. (b) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (c) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086. (d) Zhdankin, V. V. *ARKIVOC* **2009**, *1*, 1. (e) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (f) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656.

(4) (a) Khanna, M. S.; Garg, C. P.; Kapoor, R. P. *Tetrahedron Lett.* **1992**, *33*, 1495. (b) Iodine(III) variant: Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487.

(5) Reviews on hypervalent iodine-mediated asymmetric transformations: (a) Kumar, R.; Wirth, T. *Top. Curr. Chem.* **2015**, DOI: 10.1007/128_2015_639. (b) Berthiol, F. *Synthesis* **2015**, *47*, 587. (c) Parra, A.; Reboredo, S. *Chem. - Eur. J.* **2013**, *19*, 17244. (d) Ngatimin, M.; Lupton, D. W. *Aust. J. Chem.* **2010**, *63*, 653.

(6) Reviews on hypervalent iodine-mediated functionalization of carbonyl compounds: (a) Dong, D.-Q.; Hao, S.-H.; Wang, Z.-L.; Chen, C. *Org. Biomol. Chem.* **2014**, *12*, 4278. (b) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, *2011*, 517.

(7) (a) Brenet, S.; Minozzi, C.; Clarens, B.; Amiri, L.; Berthiol, F. *Synthesis* **2015**, *47*, 3859. (b) Brenet, S.; Berthiol, F.; Einhorn, J. *Eur. J. Org. Chem.* **2013**, *2013*, 8094. (c) Thérien, M.-È.; Guilbault, A.-A.; Legault, C. Y. *Tetrahedron: Asymmetry* **2013**, *24*, 1193. (d) Guilbault, A.-A.; Basdevant, B.; Wanie, V.; Legault, C. Y. *J. Org. Chem.* **2012**, *77*, 11283. (e) Guilbault, A.-A.; Legault, C. Y. *ACS Catal.* **2012**, *2*, 219. (f) Rodriguez, A.; Moran, W. J. *Synthesis* **2012**, *44*, 1178. (g) Yu, J.; Cui, J.; Hou, X.-S.; Liu, S.-S.; Gao, W.-C.; Jiang, S.; Tian, J.; Zhang, C. *Tetrahedron: Asymmetry* **2011**, *22*, 2039. (h) Farooq, U.; Schäfer, S.; Shah, A. A.; Freudendahl, D. M.; Wirth, T. *Synthesis* **2010**, *2010*, 1023. (i) Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, *2008*, 5315. (j) Richardson, R. D.; Page, T. K.; Altermann, S. M.; Paradine, S.

M.; French, A. N.; Wirth, T. *Synlett* **2007**, *2007*, 538. (k) Hirt, U. H.; Schuster, M. F. H.; French, A. N.; Wiest, O. G.; Wirth, T. *Eur. J. Org. Chem.* **2001**, *2001*, 1569. (l) Hirt, U. H.; Spingler, B.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 7674. (m) Wirth, T.; Hirt, U. H. *Tetrahedron: Asymmetry* **1997**, *8*, 23.

(8) Beaulieu, S.; Legault, C. Y. *Chem. - Eur. J.* **2015**, *21*, 11206.

(9) Basdevant, B.; Legault, C. Y. *Org. Lett.* **2015**, *17*, 4918.

(10) (a) Gonzalez-de-Castro, A.; Xiao, J. *J. Am. Chem. Soc.* **2015**, *137*, 8206. (b) VanBrunt, M. P.; Ambenge, R. O.; Weinreb, S. M. *J. Org. Chem.* **2003**, *68*, 3323. (c) Huang, B.; Gupton, J. T.; Hansen, K. C.; Idoux, J. P. *Synth. Commun.* **1996**, *26*, 165. (d) Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1993**, *34*, 4485. (e) Morton, H. E.; Leanna, M. R. *Tetrahedron Lett.* **1993**, *34*, 4481. (f) Duncan, R.; Drueckhammer, D. G. *Tetrahedron Lett.* **1993**, *34*, 1733. (g) Hsiao, C.-N.; Leanna, M. R.; Bhagavatula, L.; DeLara, E.; Zydowski, T. M.; Morton, H. E. *Synth. Commun.* **1990**, *20*, 3507.

(11) De Kimpe, N.; Verhe, R. In *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; p 496.

(12) (a) Trost, B. M.; Pinkerton, A. B. *Tetrahedron Lett.* **2000**, *41*, 9627. (b) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 8965. (c) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.

(13) See the Supporting Information for details.

(14) Basdevant, B.; Legault, C. Y. *J. Org. Chem.* **2015**, *80*, 6897.