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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b09677 • Publication Date (Web): 05 Dec 2018

ACS Publications

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Nickel-Catalyzed Reductive [2+2] Cycloaddition of Alkynes

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ABSTRACT: The nickel-catalyzed synthesis of tetrasubstituted cyclobutenes from alkynes is reported. This transformation is uniquely promoted by the use of a primary aminophosphine, an unusual ligand in nickel catalysis. Mechanistic insights for this new transformation are provided, and post-reaction modifications of the cyclobutene products to stereodefined cyclic and acyclic compounds are reported, including the synthesis of *epi*-truxillic acid.

Since the pioneering work by Reppe and Wilke on the cyclotetramerization of acetylene and ensuing ligand-influenced outcomes in catalytic cycloadditions,[1] nickel catalysis has contributed to the development of many C−C and C−heteroatom bond-forming processes.[2] Building on these early studies, nickel-catalyzed methods have led to many advances in cycloadditions, allowing the assembly of various ring sizes from simple π-components depending on the ligand system and precursors employed.[2a,2d] While the assembly of six- and eight-membered rings have been well developed, accessing cyclobutane and cyclobutene products is more limited and typically requires conjugated and activated substrates such as allenes, 1,3-enynes, or strained rings such as norbornene derivatives. The assembly of cyclobutanes and cyclobutenes by the catalytic cycloaddition of simple, non-conjugated π-components has thus proven elusive by using existing methods.

Cyclobutenes in particular are highly versatile synthetic intermediates because of their ring strain and high reactivity.[3] In addition, they are also found in many bioactive metabolites, natural products, drugs, and organic dyes.[4] In recent years, much progress has been made in strategies for the direct formation of the cyclobutene skeleton. Most commonly, the catalytic synthesis of cyclobutenes involves the use of an alkene-alkyne [2+2]-cycloaddition reaction typically involving conjugated and activated substrates (Figure 1a). Using this approach, many useful methodologies have been reported using transition metal[5-6] and Lewis acid[7] catalysis. An alternate approach involves the reductive cyclodimerization of two alkynes. This latter approach has been developed using a zirconium-mediated pyridine-directed strategy (Figure 1b),[8] but variations of this process that involve sub-stoichiometric catalyst loadings or simple alkynes that lack directing groups have not been previously described. Despite the advances realized, the development of an intermolecular catalytic route with two different alkyne coupling partners is currently not available. We recognized that such a process would provide new opportunities for rapidly building up useful synthetic intermediates from simple starting materials.

In the course of exploring new types of catalytic additions to alkynes, we unexpectedly found that the reductive dimerization of alkynes to produce cyclobutenes is the major pathway when primary aminophosphine ligands are employed. (Figure 1c). Primary β-aminophosphines have rarely been used as ligands in catalysis,[9] and are not typically employed in ligand screens of nickel-catalyzed processes. The reactivity is notable given that many nickel-catalyzed reductive transformations have been described with alkynes, whereas the alkyne reductive cyclodimerization has not previously been described. Other cycloadditions and reductive couplings involving nickel catalysis typically involve monodentate phosphines or NHC ligands,[2d] suggesting that the unique behavior of primary aminophosphines will serve as an important counterpart to these well-studied catalytic systems. Given the novelty and potential utility of the reductive cyclodimerization of alkynes in the assembly of stereo- and regiochemically-defined cyclobutenes, as well as the lack of information about the unique reactivity of nickel complexes of primary aminophosphines, we report here the development, scope, and mechanistic insights of this newly discovered process.

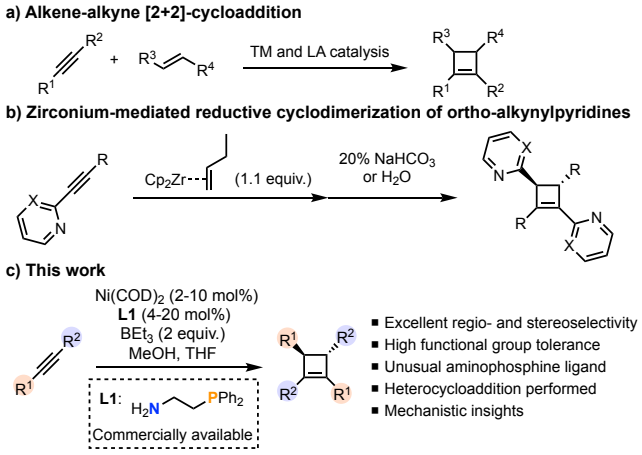
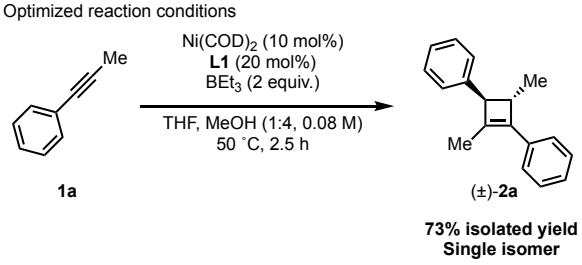


Figure 1. Approaches towards the synthesis of cyclobutenes

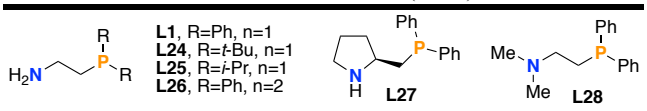
We began our investigations by studying the reaction of **1a** in a High Throughput Experimentation (HTE) platform with $Ni(COD)_2$. We screened a wide variety of ligands (**L1**-**L23**) such as aminophosphines, phosphoramidites, phosphines, amines, heterocyclic amines, NHCs and diols (Table 1, entries 4-5), several Brønsted acids such as methanol, isopropanol and

benzoic acid (Table 1, entries 4, 11-12), and reducing agents such as triethylborane and dimethylphenylsilane (Table 1, entries 4 and 13).[10] Interestingly, we only found significant amounts (>10% yield) of the desired cyclobutene **2a** with a combination of the primary aminophosphine ligand **L1**, methanol or isopropanol, and triethylborane. Notably, traces of product were found with a binary ligand system consisting of a primary amine ($BuNH_2$) and a tertiary phosphine (PPh_3), thus reinforcing the need for a tethered aminophosphine backbone. No significant amount of cyclobutene product was observed when using $NiCl_2$ reduced *in situ* by Mn or Zn (Table 1, entry 14) or the corresponding control experiments (Table 1, entries 2-3).

Table 1. Screening and optimization of the reaction conditions.[a]



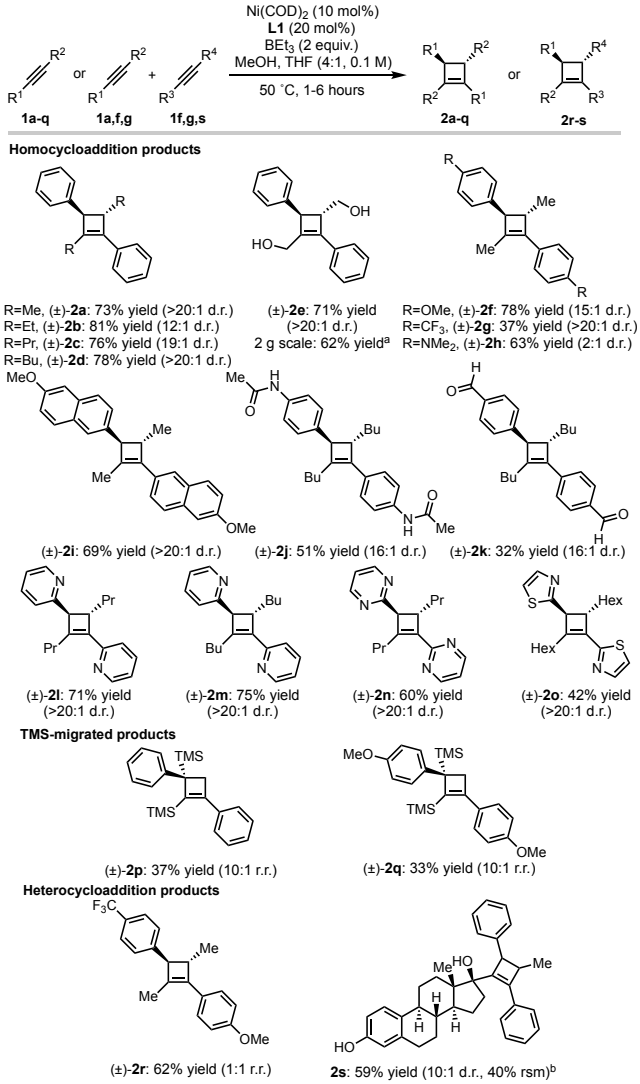
Entry	Variation from standard conditions	Yield (%)
1	None	73
2[b]	w/o $Ni(COD)_2$, **L1** or BEt_3	0
3[b]	w/o MeOH	7
4[b]	THF:MeOH (4:1)	31
5[b]	Other class of ligands instead of **L1**	<5-9
6[c]	**L24** instead of **L1**	30
7[c]	**L25** instead of **L1**	19
8[c]	**L26** instead of **L1**	11
9[c]	**L27** instead of **L1**	47
10[c]	**L28** instead of **L1**	37
11[c]	**L1**, 4 hours	61
12[b]	iPrOH instead of MeOH	12
13[b]	Benzoic acid instead of MeOH	0
14[b]	$PhMe_2SiH$ instead of BEt_3	<5
15[c]	$NiCl_2$ + Mn or Zn instead of $Ni(COD)_2$	<5



[a] Optimized reaction conditions: **1a** (0.45 mmol), $Ni(COD)_2$ (0.045 mmol), **L1** (0.09 mmol), BEt_3 (0.9 mmol), THF:MeOH (1:4 ratio, 0.08 M), 50 ºC, 2.5 h. [b] 4:1 ratio THF:MeOH was used in the HTE (10 µmol **1a**). [c] 4 hours.

Several ligands of this class (**L1**, **L24-L28**) were screened on a preparative scale (Table 1, entries 6-11), after which **L1** was revealed as the ligand of choice. After further optimization of reaction conditions,[10] the head-to-tail *trans*-cyclobutene **2a** was obtained in 73% isolated yield. Excellent regio- and stereoselectivities were observed, and all reagents and catalysts are commercially available, thus making the procedure simple and selective for the desired cyclobutenes.

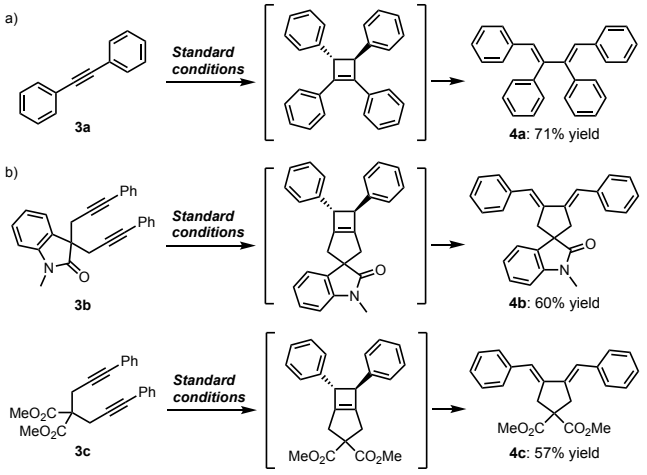
We then turned our attention to the generality of this transformation. First, a robustness screen was performed, showing a high functional group tolerance.[11] Then, a series of examples of nickel-catalyzed reductive [2+2] cycloadditions of alkynes to produce *trans*-cyclobutenes were illustrated under optimized conditions (Scheme 1). The reaction was efficient with alkynes bearing alkyl groups with different chain lengths (**2a-d**). Electronic properties of the alkyne were evaluated by introducing electron-withdrawing and electron-donating groups on the aryl moiety. Although electron rich alkynes (**2f** and **2h**) underwent coupling faster than electron-poor ones (**2g**), the desired cyclobutene was successfully obtained in all cases. The reaction was effective in the presence of unprotected polar functional groups such as an alcohol (**2e**), aldehyde (**2k**), amide (**2j**), aryl ether (**2f** and **2i**) or amine (**2h**). Alkynes bearing heterocyclic moieties such as 2-pyridyl (**2l-m**), 2-pyrimidinyl (**2n**) and 2-thiazolyl (**2o**) also gave rise to the desired cyclobutenes. TMS-alkynes showed a silyl group migration on the cyclobutene products (**2p** and **2q**).[12] Surprisingly, aldehyde/alkyne reductive coupling[13] or demethoxylation[14] pathways were not observed. The scalability of this protocol was tested through synthesis of the cyclobutene **2e** on a 2-gram scale. In this case, the catalyst loading was successfully lowered to 2 mol% and the desired cyclobutene was obtained in 62% isolated yield.



Scheme 1. Substrate scope. Isomeric ratios (d.r. and r.r.) calculated by GC-FID. [a] $Ni(COD)_2$ (2 mol %) and **L1** (4 mol %) were used. [b] See reference 15.

The suppression of alkyne homocoupling presents a clear challenge in the development of synthetically desirable reductive heterocouplings of two different alkynes.[16] In order to ex-

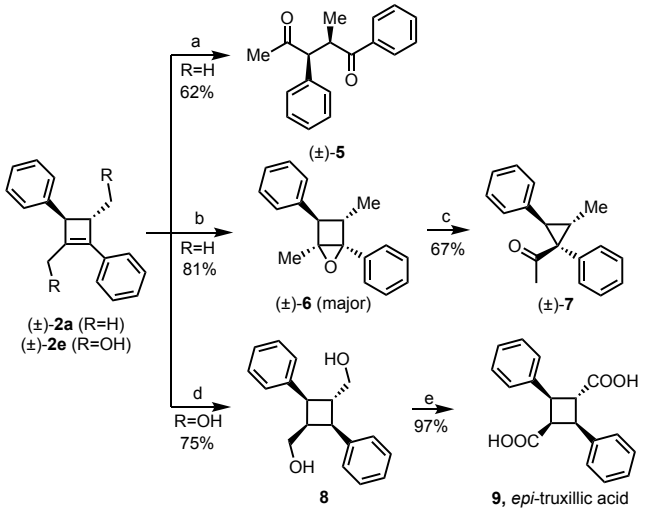
plore the feasibility of this approach, alkynes of different electronic and steric properties were examined to achieve the desired cross-reductive [2+2] alkyne cycloaddition. First, we attempted the reaction using two electronically opposed alkynes, **1g** and **1f**. To our delight, the corresponding heterocoupling product **2r** was obtained in 62% yield, accompanied by minor amounts of the homocoupling products (7% of **2g** and 21% of **2f**). Nonetheless, the two regioisomers arising from the position of the double bond in the cyclobutene ring were formed in 1:1 ratio. Then, we subjected the steroid phenyl-17α-ethynylestradiol **1s** to the reductive [2+2] cycloaddition reaction with **1a**. Due to the bulkiness of the steroid, it was unreactive towards the reductive homo-cyclodimerization. This allowed us to perform the heterocoupling in a very clean manner by slowly adding the alkyne **1a** *via* syringe pump. The corresponding heterocoupling product **2s** was obtained in 59% yield (10:1 d.r.), with 40% of the starting material **1s** being recovered. Furthermore, diphenylacetylene **3a** gave rise to the *cis*,*cis*-diene **4a** in good yield (Scheme 2a).[17a] We also attempted the cyclization of diynes to form bicyclic cyclobutenes (Scheme 2b). In both cases, the dienes **4b** and **4c** were obtained as the major products in good yields.[18] The isomer obtained in products **4a-c** suggests the formation of the *trans*-cyclobutene followed by a thermal conrotatory electrocyclic ring-opening step.[17]



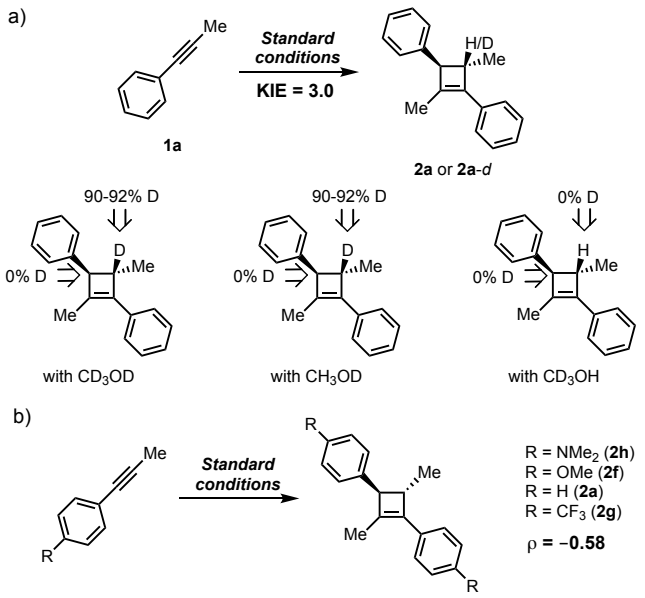
Scheme 2. a) Reductive homocoupling of diphenylacetylene. b) Reductive cyclization of diynes towards dienes.

The potential synthetic utility of this protocol was then demonstrated through the diversification of the cyclobutene products (Scheme 3). First, ozonolysis of cyclobutene **2a** afforded the stereodefined acyclic 1,4-diketone **5** as a single isomer.[19] On the other hand, epoxidation of **2a** gave rise to the cyclobutane epoxide **6** in good yield and 4:1 dr.[20] This product was then subjected to acidic conditions to perform a ring-contraction, thus affording the cyclopropyl ketone **7** in good yield and excellent diastereomeric ratio.[21] Finally, we targeted the synthesis of *epi*-truxillic acid, a naturally occurring cyclobutanedicarboxylic acid with interesting biological properties.[22,23] To our delight, the hydrogenation of cyclobutene **2e** to cyclobutane **8** took place with exquisite diastereoselectivity, with **8** being isolated as a single isomer in good yield.[24] Finally, Jones oxidation afforded the corresponding *epi*-truxillic acid **9** in quantitative yield.[25,26]

A number of experiments were conducted to shed light on the mechanistic features of this reductive cyclodimerization process. Deuterium-labelling studies displayed 90-92% deuterium incorporation using CD_3OD and CH_3OD in a regio- and stereoselective manner. On the other hand, no deuterium incorporation was observed using CD_3OH (Scheme 4a). With these results in hand, we performed the kinetic analysis of two parallel reactions run using CD_3OD and CH_3OH respectively. A primary kinetic isotope effect (KIE) of 3.0 was observed, indicating that a proton transfer is involved in the rate-determining step.[27] Motivated by the different reaction rate of electron-poor and electron-rich alkynes, we studied linear free-energy relationships to unveil potential cationic or anionic intermediates. The reactions using substrates **1a**, **1f**, **1g** and **1h** were monitored by ^{1}H-NMR to determine the corresponding kinetic behaviors (Scheme 4b). The observed Hammett plots, characterized by $\rho < 0$, suggest that a positive charge accumulates in the rate-determining step.[28]



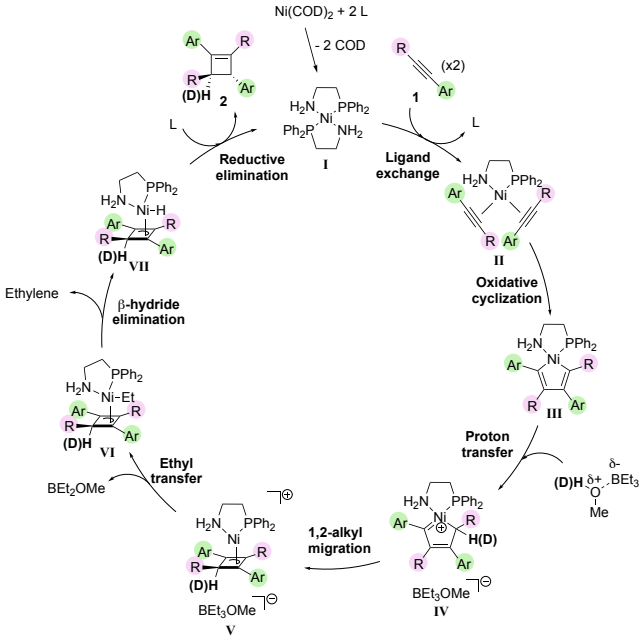
Scheme 3. Synthetic diversification of cyclobutene **2a** and **2f**. a) O_3, $CHCl_3$, −78 ºC. b) *m*-CPBA, $NaHCO_3$, $CHCl_3$, 0 ºC. c) aq HCl (0.1 M), rt. d) H-Cube, 1 mL/min, H_2 (60 bar), Pd/C (10%), 60 ºC, MeOH (0.25 M). e) CrO_3, H_2SO_4, H_2O, acetone.



Scheme 4. Mechanistic experiments.

With this mechanistic information in hand, a plausible catalytic cycle is proposed for this reaction (Scheme 5). After rapid ligand exchange with **L1** (**I**) and coordination of two alkynes to

the nickel center (**II**),[29] Ni(0) may undergo an oxidative cyclization to form the first C–C bond, generating the nickelacycle (**III**).[1,2a,30] Then, the methanol-triethylborane adduct could adduct protonate[31] the π-system generating a stabilized cationic nickel carbene **IV**.[32,33] Next, a 1,2-alkyl migration would generate the 4-membered ring and the second C–C bond (**V**).[12,34] Finally, an ethyl transfer to nickel (**VI**), β-hydride elimination[35] (**VII**) and reductive elimination[36] gives rise to the desired cyclobutene, regenerating the nickel(0) catalyst. *In situ* HRMS (ESI+) analysis of the reaction mixture using alkyne **1e** revealed a very intense *m/z* signal at 552.1609 with the characteristic isotopic distribution of a nickel species. This data suggests the presence of a nickel species that incorporates the aminophosphine and the two units of the corresponding alkyne (i.e. structures **II**–**V**). In combination with the Hammett studies and KIE experiments, the data overall is consistent with **III** being the catalyst resting state.



Scheme 5. Proposed catalytic cycle.

This overall mechanism bears analogy to [3+2] reductive cycloadditions of enals and alkynes that proceed through the protonation of enolate motifs embedded with a nickel metallacycle.[37-38] However, the only previous examples where metallacyclopentadienes are converted to cyclobutenes are the stoichiometric zirconium-mediated processes described above.[8] Notably, protonation of a Ni(II) metallacyclopentene species by a water/borate adduct[31a] and the protonation of Ni(0) species by a similar methanol/borane mixture[31b-c] have recently been proposed in the hydroalkylation and hydroarylation of allenes, styrenes and dienes under similar conditions to our study.[31] Although Ni(0) protonation would be expected to be faster than protonation of **III**, products resulting from hydroalkylation or reduction of the alkyne are only observed as minor by-products. Furthermore, exogeneous alkenes such as styrene and *E*/*Z*-β-methylstyrene are not incorporated in the cyclobutene products,[39] suggesting that nickel hydride mediated reduction of the alkyne and subsequent alkene-alkyne [2+2] cycloaddition reaction is unlikely for the production of cyclobutene products. The basis for the unique promotion exhibited by the aminophosphine **L1** is currently unclear. The role of this ligand architecture may involve features other than simple bidentate coordination, such as proton shuttling or generation of a Lewis adduct with the borane component, and further studies to understand the unique behavior of this ligand class are in progress.

In summary, a nickel-catalyzed reductive [2+2] cycloaddition reaction of alkynes towards the synthesis of *trans*-cyclobutenes has been developed. The use of an unusual primary aminophosphine ligand was key to the discovery of this new reaction. Post-reaction modifications highlighted the synthetic versatility of these products, including the synthesis of the natural product *epi*-truxillic acid.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectral data (PDF)
Crystallographic data for **4a** (CIF)
Crystallographic data for **4b** (CIF)
Crystallographic data for **10** (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support from the MINECO (grant CTQ2015-69136-R (MINECO/FEDER)) and ICIQ Foundation is gratefully acknowledged. We also thank the MINECO for support through the Severo Ochoa Excellence Accreditation 2014-2018 (SEV-2013-0319). S.C. thanks the MINECO for a Severo Ochoa FPI fellowship (BES-2015-072152). J.M. thanks the National Institutes of Health (R35-GM118133) for support. We are grateful to the ICIQ X-ray diffraction unit for the X-ray single crystal analyses of **4a**, **4b** and **10**. Prof. Ruben Martin (ICIQ) and Dr. Alex J. Nett (University of Michigan) are acknowledged for very useful discussions. We thank Mr. Sergio Fernández (ICIQ) for the assistance on the head-space analysis.

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(39) Kinetic profile of the reaction for the formation of **2c** in the presence of 1 equivalent of *E*- and *Z*-β-methylstyrene overlap with the one where no additive is added. See kinetic analyses in the Supporting Information file.

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