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# Site-Selective N-Dealkylation of 1,2,3-Triazolium Salts: A Metal-Free Route to 1,5-Substituted 1,2,3-Triazoles and Related Bistriazoles

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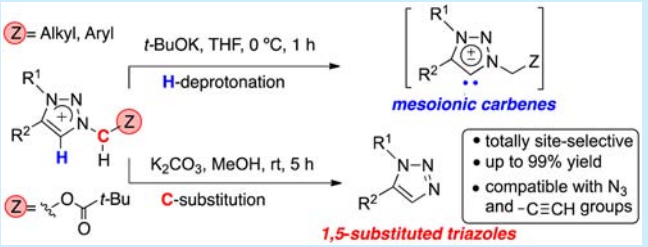
Supporting Information

**ABSTRACT:** N3-Alkylation of 1-(pivaloyloxymethyl)-1,2,3-triazoles with alkyl triflates carrying latent "click" functionality, followed by a nucleophile-promoted N1-dealkylation of the resulting strongly electrophilic intermediate triazolium salts, provides an efficient route to 1,5-disubstituted 1,2,3-triazoles. The azide and alkyne groups incorporated by N-alkylation can be submitted to further copper-catalyzed azide−alkyne and Huisgen cycloadditions to provide bis(1,2,3-triazoles) with unprecedented 1,5/1,4 substitution patterns.




1,2,3-Triazolium salts[1] have attracted increasing interest during the past decade as a result of their easy synthetic accessibility from "click" 1,4-disubstituted 1,2,3-triazoles.[2] They have been successfully used to design ionic liquids, chiral organocatalysts, and supramolecular assemblies and to prepare polymer electrolytes.[3] Surprisingly, triazolium salts have received limited attention as synthetic intermediates to prepare 1,2,3-triazole derivatives other than mesoionic carbene ligands for transition metal complexes.[4]

Recently, we became interested in the preparation of bis(1,2,3-triazoles) comprising mixed 1,5- and 1,4-substituted rings with total positional control (Figure 1). Unfortunately,

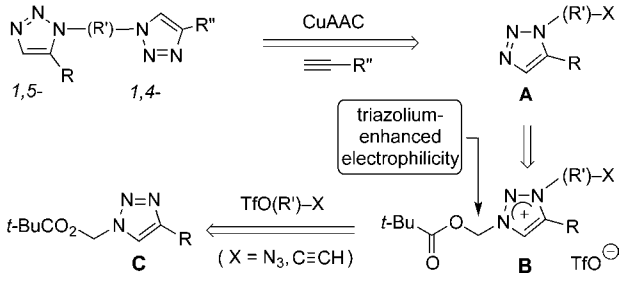



**Figure 1.** 1,5-/1,4-Bis-1,2,3-triazoles via site-selective N-dealkylation of 1-pivaloyloxymethyl-1,2,3-triazolium salts (**B**). CuAAC: Cu-catalyzed azide−alkyne cycloaddition.

the required intermediates **A** bearing azide or terminal alkyne "click" groups (X) were not directly accessible via Ru(II)-catalyzed azide−alkyne cycloadditions or related reactions to synthesize 1,5-disubstituted monotriazoles.[5]

We surmised that incorporating azide or alkyne groups to suitable 1,4-disubstituted 1,2,3-triazoles, via a Menshutkin-type N-alkylation reaction, would overcome the above-mentioned limitation, provided a dealkylation of the resulting triazolium salts could be conducted in a totally site-selective manner.[6] Sharpless and Fokin previously described *N*-pivaloyloxymethyl-1,2,3-triazoles (**C**) as base-labile N-protected 1,2,3-triazoles.[7] We now selected the novel triazolium-activated derivatives (**B**), carrying a strongly electrophilic methylene group, as potential candidates to conduct site-selective N-dealkylations of 1,2,3-triazolium salts via nucleophilic substitution reactions.

To address our objective, we first studied an optimized procedure for the N-alkylation of triazoles with alkylating agents containing "click" groups ($N_3$, C≡CH) (Table 1). N3-regioselective alkylation of 1,4-disubstituted 1,2,3-triazoles **1** occurs efficiently only with nonfunctionalized primary activated alkyl iodides or bromides.[8] Unfortunately, when more complex or functionalized alkylating groups are used, the reaction becomes sluggish or incomplete, as a result of the dynamic nature of N−C bond formation.[9] We found that alkyl triflates, freshly prepared from functionalized alcohols by treatment with triflic anhydride and $KHCO_3$ in dichloromethane,[10] efficiently alkylate 1,2,3-triazoles when the reaction is carried out in the *absence of solvent*. Complete conversions were attained by slowly evaporating an equimolar dichloromethane solution of a triazole and an alkyl triflate under nitrogen and stirring the solvent-free mixture overnight. This simple operational modification was effective to avoid the use of large excesses of alkylating reagents and/or prolonged heating that could compromise the stability of functionalized alkyl triflates.

Examples collected in Table 1 show that N-alkylation reactions with alkyl triflates under our conditions were high-yielding for a wide variety of alkylating reagents, including azide- and alkyne-functionalized ones (entries 3−4 and 6−7). The reaction was also tolerant with esters (entry 10), carbamates (entries 11 and 12), and alkynes (entry 9) present in the substrate 1,2,3-triazoles. In contrast, similar reactions

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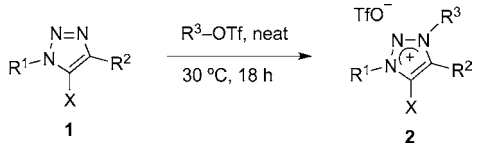
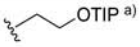
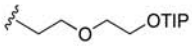
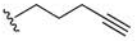
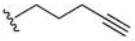
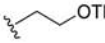
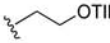
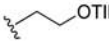
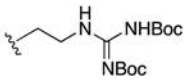
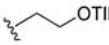
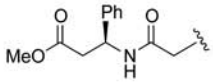
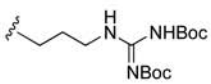
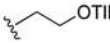
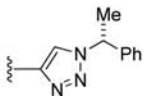
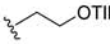
**Table 1. N-Alkylation of 1,2,3-Triazoles with Alkyl Triflates**




| entry | $R^1$ | $R^2$ | X | triazole | $R^3$ | product[a] | yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | Bn | Ph | H | **1a** |  | **2a** | 98 (20)[c] |
| 2 | Bn | Ph | H | **1a** |  | **2b** | 77 |
| 3 | Bn | Ph | H | **1a** |  | **2c** | 90 |
| 4 | Bn | Ph | H | **1a** |  | **2d** | 59 |
| 5 | Bn | Ph | H | **1a** |  | **2e** | 52 |
| 6 | Bn | Ph | H | **1a** |  | **2f** | 76 |
| 7 | 4-*t*BuC$_6$H$_4$CH$_2$- | -C$_6$H$_4$OMe-4 | H | **1b** |  | **2g** | 81 |
| 8 | Bn | Ph | I | **1c** |  | **2h** | 91 |
| 9 | Bn | -C≡CH | H | **1d** |  | **2i** | 81 |
| 10 | MeO$_2$CCH$_2$- | Ph | H | **1e** |  | **2j** | 47 |
| 11 | Bn |  | H | **1f** |  | **2k** | 92 |
| 12 |  |  | I | **1g** |  | **2l** | 77 |
| 13 |  |  | H | **1h** |  | **2m** | 81 |

[a]OTIP = 2,4,6-Triiodophenoxy group. [b]Yield of pure isolated products. [c]Reaction conversion after 48 h in a 0.4 M solution in $CH_2Cl_2$.

conducted in noncoordinating solvent solutions ($CH_2Cl_2$, MeCN) remained stagnated with poor conversions (entry 1), even after long time periods or upon heating.

With a set of triazolium salts in hand, we next studied their N-dealkylation under different conditions (Scheme 1). Bertrand first established that base-promoted N-demethylation of triazolium salt **3** to the C5-methylated triazole **5** likely occurred through the intermolecular nucleophilic attack of a mesoionic carbene formed by C5−H deprotonation of the triazolium salt.[11] To prevent carbene formation, we checked several nucleophilic reagents and found that a much milder N-dealkylation of the N1-benzyl-N3-methyl-1,2,3-triazole **2n** occurred using potassium thiophenoxide to cleave the C−N bond, albeit with very poor site selectivity (see SI, Figure S1). Importantly, the reaction provided a 68% yield of the 1,5-disubstituted triazole **6a**.

A computational calculation of the NBO charges of the N1-benzyl and N3-methyl carbon atoms in the triazolium structure **D** yielded negative values (−0.26 and −0.48, respectively). In contrast, the pivaloyloxymethyl group in structure **E** showed a positive formal charge of +0.08 at the methylene carbon, suggesting that a clean discrimination from the *N*-methyl group could be achieved upon attack by a nucleophile. Indeed, the computed $SN_2$ attack of a hydroxyl anion to **E** showed an activation barrier of $\Delta G^{\ddagger} = 4.6$ kcal·mol$^{-1}$ when the triazolium moiety acted as the leaving group (Supporing Informaion (SI), Figure S6). In agreement with these calculations, *N*-methylation of triazole **1i** with methyl triflate, followed by the "in situ" treatment of the resulting triazolium salt with $K_2CO_3$ in MeOH at room temperature, afforded exclusively the 1,5-disubstituted triazole **6a** in 79% overall yield. By conducting the same one-pot operation in the presence of MeOH-$d_4$ the C-5 deuterated triazole **7** was obtained, suggesting that a triazolylidene carbene formation could take place before the dealkylation reaction. This hypothesis was unambiguously confirmed by treating the triazolium salts **1i** and **1j** with $Ag_2O$ to form the intermediate silver carbenes and trapping them "in situ" with cyanogen iodide to form the trisubstituted iodotriazoles **8a−b** (see SI, Figures S2−S4).

To check the scope of this novel one-pot transformation of 1,4-disubstituted triazoles into 1,5-disubstituted ones, we extended the method to various alkyl triflates, focusing on functionalized triflates (Table 2). The method gave moderate to good overall yields for both aromatic (entry 1) and aliphatic (entry 2) substituents in the triazole ring, and also for alkyl triflates comprising halogen (entry 5), nitrile (entry 6), alkyne (entry 7), and azide groups (entries 8 and 9). The latter triazoles **6h**, **6i** were further reacted with phenylacetylene and



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**Scheme 1. N-Dealkylation of Triazolium Salts**

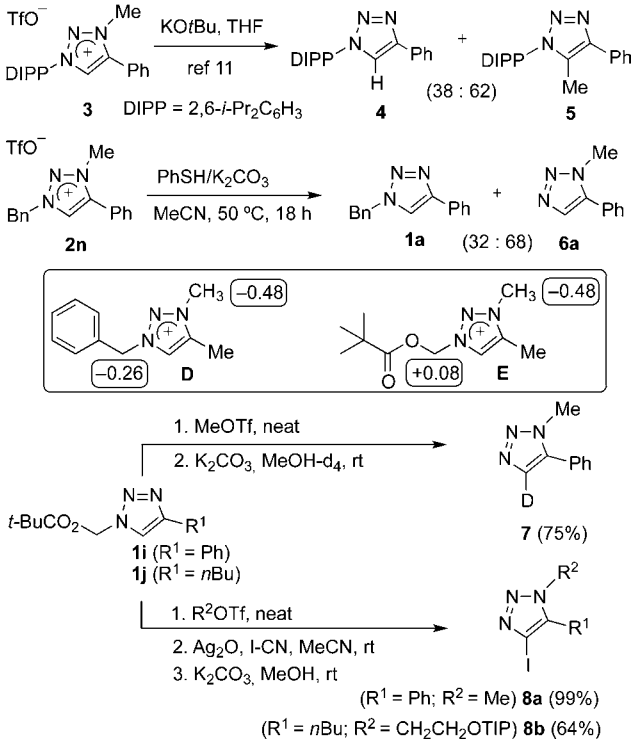
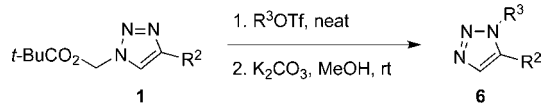
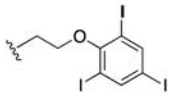



**Table 2. One-Pot Synthesis of 1,5-Disubstituted 1,2,3-Triazoles**



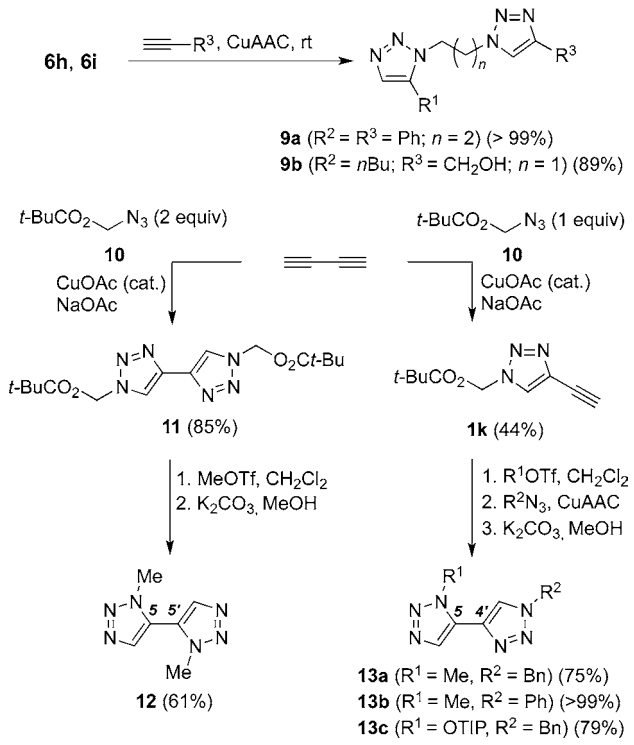

| entry | R$^2$ | triazole | R$^3$ | product (%)[a] |
|---|---|---|---|---|
| 1 | Ph | **1i** | Me | **6a** (79) |
| 2 | Bu | **1j** | Me | **6b** (83) |
| 3 | Ph | **1i** |  | **6c** (68) |
| 4 | Ph | **1i** | $CH_2CH_2Ph$ | **6d** (74) |
| 5 | Ph | **1i** | $CH_2CH_2CH_2Br$ | **6e** (52) |
| 6 | Ph | **1i** | $CH_2CH_2CH_2CN$ | **6f** (70) |
| 7 | Ph | **1i** | $CH_2CH_2CH_2C{\equiv}CH$ | **6g** (55) |
| 8 | Ph | **1i** | $CH_2CH_2CH_2N_3$ | **6h** (63) |
| 9 | Bu | **1j** | $CH_2CH_2N_3$ | **6i** (60) |

[a]Yield of pure isolated products.

propargyl alcohol under CuAAC conditions to give the 1,5/1,4-substituted bistriazoles **9a–b** in excellent yields (Scheme 2, top).

Encouraged by these results, we next examined the preparation of the poorly studied[12] or yet unkown 5,5′- and 4,5′-tethered bistriazoles **12** and **13** (Scheme 2, bottom). Accordingly, "in situ" generated butadiyne[13] was submitted to the CuAAC reaction with 1 or 2 equiv of pivaloyloxymethyl azide **10**[7a] to give, respectively, the bistriazole **11** and the 4-ethynyl-triazole **1k** as the main reaction products. When the

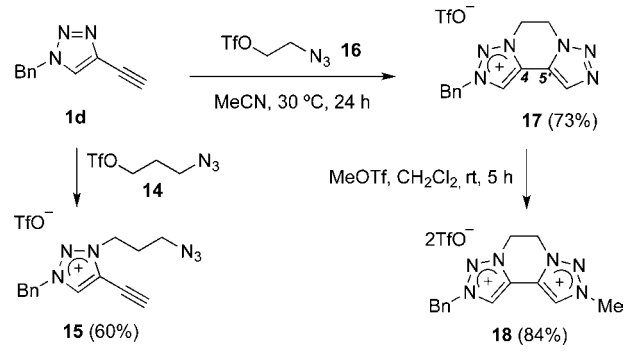
**Scheme 2. Synthesis of 1,5- and 1,4-Substituted Bis(1,2,3-triazoles)**




former was submitted to the N-alkylation/dealkylation sequence, the 5,5′-bistriazole **12** was obtained in 61% overall yield. Conversely, a similar transformation of alkyne **1k** including an additional "ultrafast" CuAAC reaction step[14] gave access to 5,4′-bistriazoles **13** in good to excellent yields. To the best of our knowledge, this is the first report of this type of heterocyclic system.

Finally, in order to extend the N-alkylation/activation methodology to the synthesis of unprecedented bridged bis-triazoles containing 1,5-substituted 1,2,3-triazole rings (e.g., tetrahydrohexaazaindacenium **17** in Scheme 3), we studied the

**Scheme 3. Synthesis of Tetrahydrohexaazaindacenium Salts**




N-alkylation of the 4-ethynyl-triazole **1d** with azidoalkyl triflates **14** and **16**. As previously demonstrated by our group, triazolium cationic alkynes undergo thermal intermolecular cycloaddition with azides about 100 times faster than analogous uncharged alkynes.[14] Therefore, we expected the intramolecular version to occur very favorably.

4-Ethynyl-triazole **1d** was readily *N*-alkylated with the 3-azidopropyl triflate **14** to the triazolium salt **15**, but the latter



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failed to give the expected intramolecular cyclization either neat or in solution under different conditions. Instead, polymer products with a polycationic backbone were produced.[15] In contrast, when the reaction was repeated using the 2-azidoethyl triflate **16** in a 0.3 M solution of MeCN at 30 °C, a clean tandem N-alkylation/cycloaddition reaction took place to give the hexaazaindacenium salt **17** in 73% yield, via intramolecular 1,5-ring closure. A computational analysis yielded an activation barrier of $\Delta G^{\ddagger}$ = 18.8 kcal·mol$^{-1}$ for the [3 + 2] cycloaddition step to **17**, whereas the analogous intermolecular cycloaddition of **1d** with methyl azide was 8 kcal·mol$^{-1}$ higher in energy (see SI, Figure S7). Interestingly, the tetrahydrohexaazaindacenium salt **17** could be further *N*-alkylated with methyl triflate to afford the nonsymmetrically substituted bis-triazolium salt **18** in 84% yield. It can be confidently anticipated that such novel dicationic triazolium salts might constitute excellent precursors of triazole dicarbenes and, therefore, of novel chelating ligands for transition metal complexation.[16]

In summary, we have shown that a variety of 1,5-substituted 1,2,3-triazoles incorporating "click"-compatible functional groups can be easily synthesized starting from 1-pivaloyloxymethyl-1,2,3-triazoles and functionalized alcohols, following a one-pot site-selective N-alkylation/N-dealkylation sequence. The method, which is metal-free and operationally very simple, takes advantage of the electrophilicity enhancement generated by the triazolium moiety on the pivaloyloxymethyl intermediates. We have also found that bis(1,2,3-triazoles) with a hitherto unknown combination of 1,5-/1,4-substitution patterns can be efficiently synthesized by combining the former methodology with CuAAC reactions or thermal intramolecular azide−alkyne [3 + 2] cycloadditions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01177.

Preparation procedures; NMR spectra of compounds **1b**, **1f−g**, **1j−k**, **2a−m**, **6−9**, **11−13**, **15**, and **17−18**; NMR studies of the N-dealkylation of **2n** and carbene intermediates for **8a**; computational geometries and energies for structures **D**, **E** (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

(1) Schulze, B.; Schubert, U. S. *Chem. Soc. Rev.* **2014**, *43*, 2522.
(2) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (d) Haldón, E.; Nicasio, M. C.; Pérez, P. J. *Org. Biomol. Chem.* **2015**, *13*, 9528.
(3) (a) Aizpurua, J. M.; Fratila, R. M.; Monasterio, Z.; Pérez-Esnaola, N.; Andreieff, E.; Irastorza, A.; Sagartzazu-Aizpurua, M. *New J. Chem.* **2014**, *38*, 474. (b) Obadia, M. M.; Drockenmuller, E. *Chem. Commun.* **2016**, *52*, 2433.
(4) (a) Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Monasterio, Z. In *Topics in Heterocyclic Chemistry*; Dehaen, W., Bakulev, V. A., Eds.; Springer-Verlag; Heidelberg, 2014; Vol. *40*, pp 211−268. (b) Mercs, L.; Albrecht, M. *Chem. Soc. Rev.* **2010**, *39*, 1903.
(5) For selected references, see: (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (b) Lamberti, M.; Fortman, G. C.; Poater, A.; Broggi, J.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P. *Organometallics* **2012**, *31*, 756. (c) Smith, C. D.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 4826. (d) Li, Y.; Qi, X.; Lei, Y.; Lan, Y. *RSC Adv.* **2015**, *5*, 49802. (e) Hong, L.; Lin, W.; Zhang, F.; Liu, R.; Zhou, X. *Chem. Commun.* **2013**, *49*, 5589. (f) Thomas, J.; Jana, S.; John, J.; Liekens, S.; Dehaen, W. *Chem. Commun.* **2016**, *52*, 2885.
(6) This approach was first implemented by Koguchi on *N*-(3,4-dimethoxybenzyl)-1,2,3-triazolium salts, but the conditions required for the oxidative dealkyltion of the benzyl group [$Ce(NH_4)_2(NO_3)_6$, DMF, 120 °C, 13−24 h] were incompatible with functionalized substituents. (a) Koguchi, S.; Izawa, K. *Synthesis* **2012**, *44*, 3603. (b) Koguchi, S.; Izawa, K. *ACS Comb. Sci.* **2014**, *16*, 381.
(7) (a) Loren, J. C.; Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Synlett* **2005**, 2847. (b) Saftić, D.; Vianello, R.; Žinić, B. *Eur. J. Org. Chem.* **2015**, *2015*, 7695.
(8) Yacob, Z.; Liebscher, J. In *Topics in Heterocyclic Chemistry*; Dehaen, W., Bakulev, V. A., Eds.; Springer-Verlag; Heidelberg, 2014; Vol. *40*, pp 167−201.
(9) Obadia, M. M.; Mudraboyina, B. P.; Serghei, A.; Montarnal, D.; Drockenmuller, E. *J. Am. Chem. Soc.* **2015**, *137*, 6078.
(10) (a) Hanack, M.; Fuchs, K.-A.; Collins, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 4008. (b) Bolje, A.; Kosmrlj, J. *Org. Lett.* **2013**, *15*, 5084.
(11) Bouffard, J.; Keitz, B. K.; Tonner, R.; Guisado-Barrios, G.; Frenking, G.; Grubbs, R. H.; Bertrand, G. *Organometallics* **2011**, *30*, 2617.
(12) (a) Angell, Y.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3649. (b) González, J.; Pérez, V. M.; Jiménez, D. O.; Lopez-Valdez, G.; Corona, D.; Cuevas-Yañez, E. *Tetrahedron Lett.* **2011**, *52*, 3514.
(13) Janka, M.; Anderson, G. K.; Rath, N. P. *Organometallics* **2004**, *23*, 4382.
(14) Monasterio, Z.; Sagartzazu-Aizpurua, M.; Miranda, J. I.; Reyes, Y.; Aizpurua, J. M. *Org. Lett.* **2016**, *18*, 788.
(15) Mudraboyina, B. P.; Obadia, M. M.; Abdelhedi-Miladi, I.; Allaoua, I.; Drockenmuller, E. *Eur. Polym. J.* **2015**, *62*, 331.
(16) (a) Aizpurua, J. M.; Sagartzazu-Aizpurua, M.; Monasterio, Z.; Azcune, I.; Mendicute, C.; Miranda, J. I.; García-Lecina, E.; Altube, A.; Fratila, R. M. *Org. Lett.* **2012**, *14*, 1866. (b) Guisado-Barrios, G.; Bouffard, J.; Donnadieu, B.; Bertrand, G. *Organometallics* **2011**, *30*, 6017.



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