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Metal-Free 1,5-Regioselective Azide–Alkyne [3+2]-Cycloaddition

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On the occasion of the 10th anniversary of click chemistry

Abstract: [3+2]-cycloaddition reactions of aromatic azides and silylated alkynes in aqueous media yield 1,5-disubstituted-4-(trimethyl-silyl)-1*H*-1,2,3-triazoles. The formation of the 1,5-isomer is highly favored in this metal-free cycloaddition, which could be proven by 1D selective NOESY and X-ray investigations. Additionally, DFT calculations corroborate the outstanding favoritism regarding the 1,5-isomer. The described method provides a simple alternative protocol to metal-catalyzed "click chemistry" procedures, widening the scope for regioselective heavy-metal-free synthetic applications.

Keywords: alkynes · azides · click chemistry · cycloaddition · regioselectivity

Introduction

The classical thermal Huisgen [3+2]-cycloaddition[1] between azides and alkynes, formerly of not much value in synthetic applications owing to poor regioselectivity, experienced a renaissance after the findings of Tornøe and Sharpless, and their respective co-workers, as a prominent example for a "click"-concept reaction.[2] This Cu^{I}-catalyzed variant (CuAAC) yields regiospecifically 1,4-disubstituted 1,2,3-triazoles under mild conditions. On the contrary, ruthenium catalysis has been developed providing the complementary 1,5-disubstituted triazoles (RuAAC).[3] However, conditions required for RuAAC are often harsh compared to those for copper catalysis. Therefore, more recent investigations have increasingly focused on new methods to yield, efficiently, 1,5-disubstituted 1,2,3-triazoles under mild conditions.[4] Regrettably, there are only very few reports available that provide 1,5-regioselective azide–alkyne cycloaddition protocols under heavy-metal-free conditions.[5] The increased interest in 1,2,3-triazoles is based on their molecular properties, for example, biological activity[6] or the ability for metal coordination.[7] Moreover, the dipolar cycloaddition of azides and alkynes provides a wide scope and fidelity. In this context, in addition to the apparent metal-catalyzed techniques, efficient metal-free cycloadditions have also been developed successfully.[8] The most prominent example, the "strain promoted" 1,3-dipolar cycloaddition (SPAAC) of highly reactive cyclooctynes with azides, allows a fast and efficient functionalization of, for example, biological samples.[9] However, this method features only very limited regioselectivity.[10] In addition, owing to the complexity of the required substrates, this method is rarely appropriate to straightforward synthetic applications. To overcome the problem of low regioselectivities observed in the majority of thermal azide–alkyne cycloadditions,[11] regiodirecting methods with substituted unstrained alkynes, using electronic as well as steric effects, can be targeted.[2d,12] For instance, trimethylsilyl (TMS)-acetylenes as dipolarophiles in azide–

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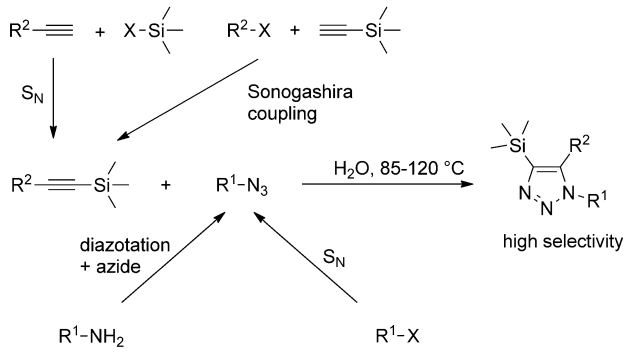
alkyne cycloadditions have been applied.[13] Notably, the TMS-group can lead to a high selectivity considering 4-TMS-triazoles. Initially, a combination of steric interactions and electronic effects, which lead to an increase of the electrophilicity of the β-carbon of alkynes, was assumed.[14] However, the regiocontrolling parameters of the TMS group have not been confirmed in detail up to now. Even more importantly, silylated triazoles have been recognized as valuable building blocks in cross-coupling reactions.[15]

Here, a systematic investigation of cycloadditions of substituted TMS-acetylenes with azides is reported (Scheme 1). It is noteworthy that using water as a solvent/dispersant for



Scheme 1. Schematic representation of synthetic pathways to 1,5-disubstituted-4-trimethylsilyl-1,2,3-triazoles by metal-free 1,3-dipolar cycloaddition.

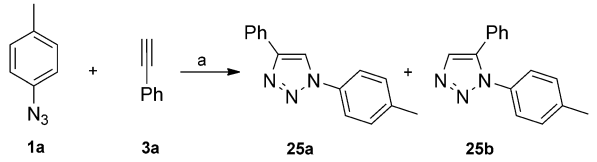
dipolar cycloadditions entails economic advantages, is easy to handle (e.g., simplified purification), and is known to have an influence on the reactivity as well as the regioselectivity of cycloadditions.[16]

Results and Discussion

In the context of the trimethylsilyl regiodirected azide–alkyne cycloaddition approach, the required trimethylsilylacetylene derivatives[17] were synthesized by a simple route through Sonogashira cross-coupling reactions. While the trimethylsilyl group is a standard protecting group in classical alkynyl coupling protocols, this method directly provides the desired precursors without additional expense. In order to avoid metal contaminations from the used catalyst, which may subsequently catalyze dipolar cycloadditions, all alkyne derivates were distilled prior to use. As a matter of course, terminal alkynes were converted to the corresponding trimethylsilyl compounds by nucleophilic substitution with trimethylchlorosilane under basic conditions (see Supporting Information).

Aromatic azides were also synthesized by a metal-free procedure. In the first step, aniline derivatives were converted to diazonium salts using a standard protocol.[18] Subsequently, the resulting diazonium salts were treated with aqueous solutions of sodium azide and sodium acetate. The resulting azide compounds **1a–f** were isolated in good to very good yields (see Supporting Information).

The initial studies were focused on the thermal 1,3-dipolar cycloaddition between *p*-tolyl azide **1a** and phenylacetylene **3a**, an example well-known for being unselective (Scheme 2).[11] Expectedly, the reaction of *p*-tolyl azide **1a**



Scheme 2. Schematic representation of the azide–alkyne [3+2] cycloaddition of **1a** and **3a**. a) H_2O, 85 °C, 22 h, 85 %, **25a**/**25b** = 49:51.

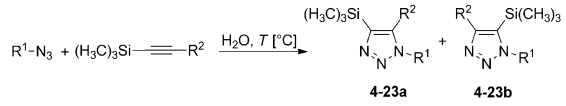
and phenylacetylene **3a** in the presence of water resulted in the desired triazole compounds (later referred to as **25a,b**, see Table 2). In contrast to the observations of Wang and co-workers,[19] both isomers were found in an almost 1:1 ratio in the crude product.

These results were used as the starting point to privilege one regioisomer by the use of trimethylsilylacetylene derivates (see Table 1). Intriguingly, the reaction of **1a** with unsubstituted trimethylsilylacetylene **2a** afforded the 4-silylated isomer **4a** in good yield and excellent regioselectivity.[20] In analogy, the conversion of 2-(trimethylsilyl)-phenyl-acetylene **2c** as dipolarophile and *p*-tolyl azide **1a** gave the 1,5-disubstituted 4-(trimethylsilyl)triazole **5** in high 1,5-regioselectivity (97 %).

In order to stress the regiodirecting influence of the TMS group, we next installed a sterically hindered substituent R^2 at the alkyne compounds. If the steric effect of the trimethylsilyl-group is the dominant factor, the 1,5-regioselectivity should decrease with an increase of the steric demand of this substituent. Therefore, mesityl-2-(trimethylsilyl)-acetylene **2b** was synthesized through Sonogashira reaction with mesityliodide. Surprisingly, the 1,3-dipolar cycloaddition between **2b** and **1a** also provided the 1,5-isomer (**6a**) with an even greater 1,5-regioselectivity (99 %). It seems that the

Abstract in German: [3+2]-Cycloadditionen zwischen Aziden und silylierten Alkinen führen in wässrigen Lösungsmitteln zu 1,5-disubstituierten 4-(Trimethylsilyl)-1*H*-1,2,3-triazoles. In dieser schwermetallfreien Cycloadditions-variante ist die Bildung des 1,5-Regioisomers besonders bevorzugt. Dies konnte durch selektive NOESY-Experimente (1D) und Einkristall-Röntgendiffraktometrie bestätigt werden. Weiterhin wurde die herausragende 1,5-Regioselektivität durch DFT-Berechnungen unterstützt. Die hier beschriebene Methode stellt eine einfache Alternative zu metall-katalysierten "Click-Chemie"—Synthesewegen dar—eine 1,5-regioselektive [3+2]-Cycloaddition für schwermetallfreie Syntheseanwendungen.

Table 1. Schematic representation and selected details of the discussed azide-alkyne 1,3-dipolar [3+2] cycloadditions.



R1: **1a** = *p*-Tolyl, **1b** = 1-Adamantyl, **1c** = 3,4,5-$(CH_3O)_3$-Ph, **1d** = C_6F_5, **1e** = Mesityl, **1f** = *p*-Br-Ph

R2: **2a** = H, **2b** = Mesityl, **2c** = Ph, **2d** = *o*-Tolyl, **2e** = *p*-Anisyl, **2f** = *n*-Bu, **2g** = 2-Pyridyl, **2h** = COOEt, **2i** = C_6F_5, **2j** = *p*-NO_2-Ph, **2k** = *p*-CF_3-Ph, **2l** = *p*-HO-CH_2-Ph

Triazole	R^1	R^2	*T* [°C]	*t* [h]	Yield [%][b]	Ratio a/b [%][h] ([i])
4	**1a**	**2a**	85	5	80	>95 a[a] (>99 a)[k]
5	**1a**	**2c**	85/110	15+16[c]	86	>95 a (97 a)
6	**1a**	**2b**	85/110	22+3[c]	60	>95 a (99 a)
7	**1b**	**2b**	120	46	64	>93 a[e] (>99 a)
8	**1a**	**2d**	110	21	84	>95 a (99 a)
9	**1a**	**2e**	85/110	22+20	85	95 a (97 a)
10	**1a**	**2f**	85	25	64	>94 a[e] (>99 a)
11	**1a**	**2g**	85[m]	70	31[f]	≥94 a[d] (99 a)
12	**1a**	**2h**	85	41	86	>91 a[d] (97 a)
13	**1a**	**2i**	110	16	81	≥90 a[d] (96 a)
14	**1c**	**2b**	110	17	78	>95 a (>99 a)[k]
15	**1d**	**2b**	110	30	61	>91 a[e] (98 a)
16	**1e**	**2b**	110	8.5	26[f]	n.d. (97 a)
17	**1c**	**2j**	85	17	74	≥94 a (>99 a)[k]
18	**1d**	**2j**	110	17	28[f]	87 a[g] (97 a)
19	**1e**	**2j**	85	20	92	87 a (91 a)
20	**1c**	**2k**	110	22	39[f]	≥93 a (98 a)
21	**1e**	**2k**	85	28	59[f]	n.d. (90 a)
22	**1b**	**2k**	110	42	66	≥92 a (98 a)
23	**1f**	**2l**	100	18	91	>95 a (>99 a)[k]

[a] No byproduct was observed in ^{1}H NMR. [b] Yields of unpurified products. [c] First period at 85 °C, second period at 110 °C. [d] Regioselectivity is expected to be higher, signal in the ^{1}H NMR spectrum shows participation of an additional impurity. [e] Interference with desilylated compound cannot be completely ruled out. [f] Yield of isolated product. [g] Desilylated product. [h] ^{1}H NMR quantified. [i] GC-MS/FID quantified. [k] No byproduct was observed in GC-MS/FID chromatogram. [m] Run in DMSO; n.d.: not determined.

steric bulkiness of the mesityl group has no significant influence on the 1,5-regioselectivity of the triazole ring formation. In addition, the azide **1a** was changed to 1-adamantylazide **1b** in order to induce higher steric constraints. Even so, the reaction between **1b** and mesityl-2-(trimethylsilyl)-acetylene **2b** afforded the corresponding triazole derivate **7** in moderate yield, but still with very high 1,5-regioselectivity (>99%). These first attempts illustrated a remarkable influence of the TMS group in alkynes with respect to the regioselectivity of these kinds of 1,3-dipolar cycloaddition reactions. It seems that the TMS group clearly favors the 4-position in the 1,4,5-trisubstituted triazole derivates to a great extent, independent of the steric bulkiness of substituents.

A possible electronic influence of the TMS moiety on the regioselectivity in 1,3-dipolar cycloadditions, however, requires a more detailed study using *p*-tolyl azide **1a** and different substituted ethynyltrimethylsilanes. Starting with *o*-tolyl substituted trimethylsilylacetylene **2d**, the triazole **8a** was obtained with high 1,5-regioselectivity (99%). Compared to the triazole **6a**, the NMR and GC results showed that no significant change in the regioselectivity occurred. The inductive effect of the methyl group has no influence on the regioselectivity.

In all cases, single crystal X-ray diffractometry or NMR spectroscopy has been utilized to determine the regiochemistry of the silylated triazoles.

Regrettably, the heteronuclear long-range coupling of carbons and hydrogens between R^1 and R^2 could not be observed using the HMBC experiment owing to their large distance. Therefore, NOESY experiments were performed to determine the substitution pattern of the triazoles. The regiochemistry of the major isomer was confirmed by the characteristic NOE correlation. In this context, 1D selective NOESY experiments could be accomplished. Exemplarily, a 1D selective NOESY spectrum is shown for compound **6a** in Figure 1. Excitation of the CH protons in the *p*-tolyl

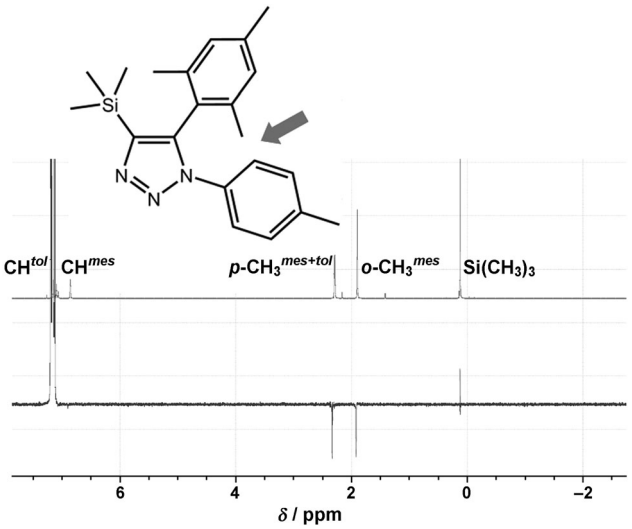


Figure 1. 1D selective NOESY spectrum (bottom) and ^{1}H NMR spectrum (top) for triazole **6a**.

group resulted in a NOE of the *o*-methyl protons in the mesityl group, indicating that the 1,5-isomer was formed. Notably, selective NOE experiments provide a high performance in terms of time efficiency.

In order to gain a deeper understanding of the electronic influence of the TMS group on the regioselectivity, a stronger electron-releasing group with marginal steric hindrance was installed at the trimethylsilylacetylene unit.

Thus, triazole **9a** was synthesized by the reaction of *p*-tolyl azide **1a** with (*p*-anisylethynyl)trimethylsilane **2e**. In comparison to **6a**, a similar ratio of regioselectivity was measured (97%). Consequently, an aromatic group that contains ring substituents with a strong electron releasing effect has no decreasing influence on the regioselectivity. As a consequence, the electronic influence of electron-withdrawing groups in the trimethylsilylacetylene unit on the regioselectivity was investigated. Thus, triazole **11a** was formed between 2-(trimethylsilylethynyl)pyridine **2g** and **1a.** This reaction was carried out in DMSO owing to the side reactions observed in water such as TMS cleavage. This

effect can be explained by the basicity of the pyridine moiety. However, the reaction proceeded much slower in DMSO than in water, but still afforded the 1,5-regioisomer (99%) of **11** highly selectively. Using substituted TMS-acetylenes providing stronger electron-withdrawing groups, such as ester (**2h**) or pentafluorphenyl (**2i**), a slight decrease of the regioselectivity was observed. Treatment of the TMS-acetylene derivates **2h** and **2i** with **1a** yielded triazoles **12a** and **13a** with a regioselectivity of over 90% of the 1,5-isomer, respectively. It should be noted that the effect of electron-withdrawing groups is small, but cannot be neglected.

In order to delve deeper into the electronic influence of the substituents R^1 and R^2 on the triazoles' substitution preference, 1,3-dipolar cycloadditions were investigated by using different substituted azides. For this purpose, the scope of the developed protocol was further extended to the synthesis of the 1,4,5-trisubstituted triazoles **14**, **15**, and **16** by using mesityl-2-(trimethylsilyl)acetylene **2b** as dipolarophile. The attempted reaction between **2b** and 3,4,5-trimethoxy-phenylazide **1c** (strong electron-releasing group) afforded the triazole **14a** with excellent regioselectivity. Not even traces of the regioisomer could be detected by the applied techniques (GC-MS/FID). It should be mentioned that the formation of **14a** represents the most selective reaction in the present study. Also ^{1}H NMR spectroscopy indicated that no further product was formed.

A related protocol which involves **2b** and mesityl azide **1e** resulted in the expected triazole **16a**, which was isolated in low yield, but a high regioselectivity (97%) could be observed. Moreover, the azide derivate **1d**, bearing a pentafluorophenyl moiety, was reacted with **2b** to afford the triazole **15a** in a ratio of regioselectivity of 98% of the 1,5-isomer. These results show that the 1,5-regioselectivity did not decrease significantly by introducing electron-withdrawing groups as the azide substituents.

Based on these findings we focused on the use of TMS-acetylenes with electron-withdrawing groups in reactions with different azides. Therefore, trimethyl((*p*-nitrophenyl)-ethynyl)silane **2j** was applied. The reaction of **2j** with 3,4,5-trimethoxy-phenylazide **1c** yielded the corresponding triazole **17a** with very high 1,5-regioselectivity. No byproduct could be detected in the GC chromatogram. By contrast, the treatment of **2j** with perfluorophenylazide **1d** resulted in the formation of **18a** with 97% 1,5-regioselectivity. Regarding this case, it should be pointed out that both regioisomers were obtained in the desilylated form. A more remarkable decrease in the 1,5-regioselectivity was found in the reaction between **2j** and mesitylazide **1e** with a value of 91% (triazole **19a**). The chosen examples show that the introduced electron-withdrawing group in the TMS-acetylene decreases the 1,5-regioselectivity. This effect is increased by introducing an electron-withdrawing group (triazole **18a**) or a sterically demanding group (triazole **19a**) in the azide. In analogy to the approach involving alkyne **2j**, 1,3-dipolar cycloadditions between trimethyl((*p*-trifluoro-methyl-phenyl)-ethynyl)-silane **2k** as dipolarophile and azides **1c**, **1e**, and **1b** as dipoles have been performed, providing similar results with respect to the regiodirecting behavior (triazoles **20**–**22**). These results confirmed the assumption that the preference of the 1,5-substitution pattern is slightly decreased by using an electron-withdrawing group in the TMS-acetylene. The preference regarding 1,5-disubstituted triazoles is increasingly disfavored by introducing a sterically demanding group in the azide, for example, a mesityl group. Surprisingly, the adamantyl substituent shows a much weaker effect than mesityl. Additionally, it appears that azides bearing electron-withdrawing moieties slightly disfavor the 1,5-regiopreference between trimethylsilylalkynes and azides (see triazoles **13**, **15**, or **18**). By contrast, azides attached to electron-releasing groups favor 1,5-regioselectivity, exclusively (see triazole **14** and **17**).

These investigations have shown that the developed method represents a powerful and versatile tool for the efficient synthesis of 1,5-disubstituted-4-silylated-1*H*-1,2,3-triazoles in high to excellent 1,5-regioselectivity. Additionally, the applicability of this potent 1,3-dipolar cycloaddition type was extended to a TMS-acetylene derivative functionalized with a benzylic alcohol group inspired by this study. Exemplarily, the triazole **23a** bearing three different functionalities (benzylic alcohol, bromine, and trimethylsilyl) for potential further modifications could be obtained in high yield and with excellent 1,5-regioselectivity (>99%) (see Supporting Information). Single-crystal X-ray analysis confirmed the assumed 1,5 substitution pattern; the ORTEP drawing of **23a** is shown in Figure 2.

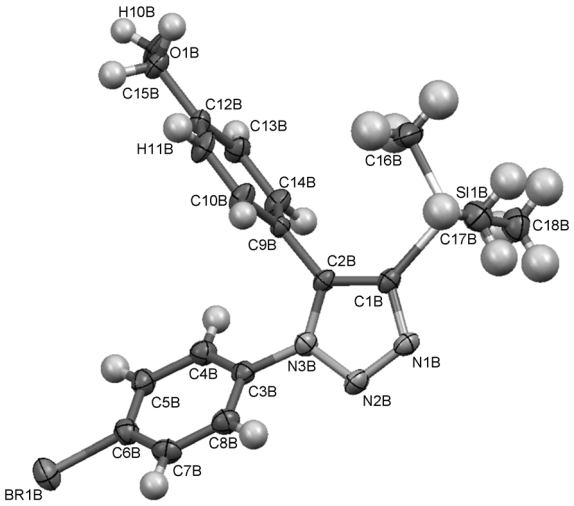
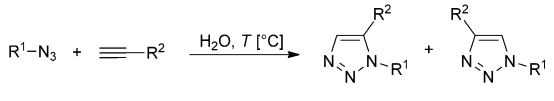


Figure 2. ORTEP diagram of **23a.**

In order to provide concrete evidence about the influence of the TMS group on the regioselectiviy in the 1,3-dipolar cycloadditions studied, reactions without the TMS-group have been performed (see Table 2).

According to earlier reports, water is expected to effect changes in the regioselectivity of thermal azide–alkyne cycloadditions.[19] However, our first findings are partially non-

Table 2. Schematic representation and selected details of the discussed azide-alkyne 1,3-dipolar [3+2] cycloadditions.



R^1: **1a** = *p*-Tolyl, **1c** = 3,4,5-$(CH_3O)_3$-Ph, **1d** = C_6F_5, **1g** = Ph

R^2: **3a** = Ph, **3b** = Mesityl, **3h** = COOEt

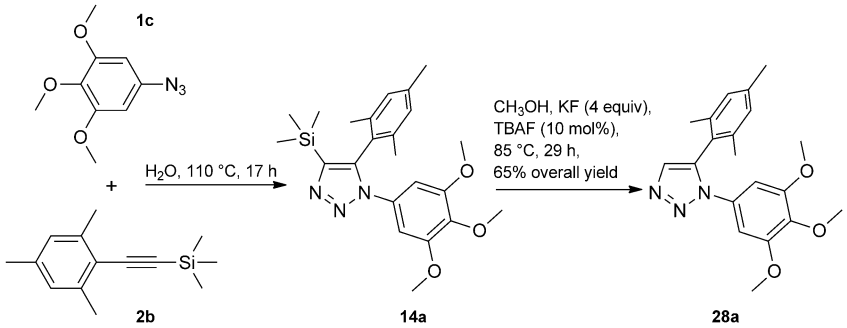
Triazole	R^1	R^2	T [°C]	t [h]	Yield [%][a]	Ratio a/b [%][c] ([b])
24	**1g**	**3a**	85	26	82	47 (49)
25	**1a**	**3a**	85	25	90	42 (51)
26	**1a**	**3h**	85	4.5	87	22 (22)
27	**1a**	**3b**	110	25	79	86 (n.d.)
28	**1c**	**3b**	110	24	84	94 (97)
29	**1c**	**3a**	110	24	93	66 (67)
30	**1d**	**3h**	85	5	92	22 (23)

[a] Yields of unpurified products. [b] GC-MS/FID quantified. [c] ^{1}H NMR quantified; n.d.: not determined.

compliant with this postulation. Using *p*-tolylazide **1a** or phenylazide **1g** as azide, the reactions yielded approximately 1:1 mixtures of the triazoles **24** and **25**, respectively. By contrast, the reaction between **1a** and ethyl propiolate **3h** resulted in a preference of the 1,4-isomer of the triazole derivate **26**. The obtained regioisomeric ratio is 78:22 and is comparable to the result reported by Wang and co-workers.[19] In order to demonstrate that the use of sterically demanding groups with only a moderate electron-releasing character is expected to direct the cycloaddition towards 1,4-substituted triazoles, the reaction between mesitylacetylene **3b** and **1a** was explored. Surprisingly, the conversion afforded the triazole **27**, notably in high 1,5-regioselectivity (86%). In a related reaction, treatment of **3b** with 3,4,5-trimethoxyphenylazide **1c** afforded the triazole **28** in an even higher 1,5-regioselectivity (97%). Both the azide and the alkyne substituent are supposed to favor the 1,5-position in triazoles **28**, and this tendency was further proven by the reaction between the azide derivate **1c** and phenylacetylene **3a**. The regioselectivity decreased significantly to 67%, however, still an excess of the 1,5-regioisomer was noted. This result illustrated that despite the steric demand of the mesityl moiety, a strong electronic preference for 1,5-disubstitution is present. On the basis of these observations, the excellent 1,5-regioselectivity in the formation of triazole **14a** is comprehensible. All three substituents have a convergent influence on the regioselectivity, whereas the trimethylsilyl group has the most powerful effect, substituting the 4-position in the triazole ring exclusively. In contrast, the mesityl-group has a strong preference to the 5-position as described above. Additionally, an electron-releasing substituent in azide or acetylene also supports a regiopreference towards the 1,5-substitution pattern in the triazole ring. In a related approach, these findings have been confirmed by a 1,3-dipolar cycloaddition between azide and an acetylene, both containing an electron-withdrawing group. As supposed, the treatment of ethyl propiolate **3h** and pentafluorophenyl azide **1d** afforded the triazoles **30** with an excess of the 1,4-isomer. Compared to the formation of triazoles **26**, no significant difference in the ratio of 1,4-selectivity was observed. It seems that in the case of unsilylated acetylene derivates, an increase in the ratio of 1,4-selectivity is achieved by the use of electron-withdrawing groups in the acetylene derivates. An electron-withdrawing group attached to the azide does not seem to have a substantial additional influence on the 1,4-regioselectivity (see triazoles **30**).

Surprisingly, during the investigation of the trimethylsilyl-regiodirected azide–alkyne cycloaddition, the TMS group of the generated 1,4,5-substitutetd triazoles **4**–**23** and of the respective alkynes are very stable under the applied hydrolytic conditions (see Table 1). Finally, in order to demonstrate that the cleavage of the TMS group of the synthesized 1,4,5-substituted triazoles **4**–**23** is feasible, the reaction between 3,4,5-trimethoxy-phenylazide **1c** and (mesitylethynyl)trimethylsilane **2b** was used.

Corresponding to earlier reports, TMS modified triazoles can be desilylated by using potassium fluoride and catalytic amounts of tetrabutylammonium fluoride (TBAF) in methanolic solution (Scheme 3).[22] The attempted desilylation reaction of the silylated triazole **14a** was carried out in one pot, forming the desilylated 1,5-disubsituted triazole **28a** in good yield (see Supporting Information).



Scheme 3. Schematic representation of the one pot desilylation of **14a** to **28a**.

Furthermore, DFT calculations were performed in order to gain deeper insights regarding the regiodirecting role of the trimethylsilyl group in 1,3-dipolar cycloadditions of azides and alkynes.[9,23] Recently, Houk and co-workers reported that the energy to distort 1,3-dipoles and dipolarophiles to their transition state geometries is related to the activation energies of these kinds of 1,3-dipolar cycloaddi-

tion.[24] In addition, Houk has also shown by DFT calculations that the mechanism of 1,3-dipolar cycloadditions of phenyl azide and cyclooctyne derivates are concerted and nearly synchronous. This observation is supported by the performed calculations. The DFT calculations of **6a,b** reveal that the activation barrier of the 1,5-substituted 4-(trimethylsilyl) triazole **6a(ts)** is 23.2 kJ mol^{-1} lower compared to 1,4-regioisomeric transition state **6b(ts)** and, therefore, consistent with the synthetic observations. The activation energies for both transition states (179.1 kJ mol^{-1} for **6b(ts)** and 155.9 kJ mol^{-1} for **6a(ts)**; see Figure 3 and Table 3) are very high owing to the distortion energies (Table 4) of the azides and of acetylene compounds based on their relaxed starting geometries. The N-N-N dipole angles of the azide reactant distort to 134.7° (**6a(ts)**) and 135.4° (**6b(ts)**), starting from a relaxed azide angle of 173.3°. The Si-C-C angle of the silylated acetylene is deformed from nearly 180° to 145.8° (**6a(ts)**) and 151.7° (**6b(ts)**) (Figure 3 and Supporting Information).

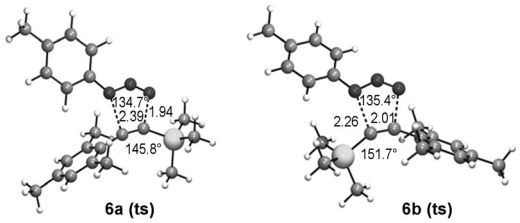


Figure 3. B3LYP/6-311++G(2d,2p) calculated transition state structures of **6a(ts)** and **6b(ts)** (see also Supporting Information).

Table 3. Calculated free energies (in kJ mol^{-1}) and predicted regioisomeric ratios of selected azide-alkyne 1,3-dipolar [3+2] cycloadditions.

				Gas phase		SMD solvation model		C-PCM solvation model	
	R^1	R^2	Isomer	ΔG^+	ΔG	ΔG^+	ΔG	ΔG^+	ΔG
6	**1a**	**2b**	a (100)[a]	155.9	−90.9	155.2	−104.9	154.1	−98.1
			b (0)[a]	179.1	−86.7	180.3	−113.1	184.0	−97.5
13	**1a**	**2i**	a (99)[a]	153.1	−108.5	161.7	−121.8	159.4	−112.5
			b (1)[a]	169.4	−107.5	172.3	−127.0	173.6	−115.9
14	**1c**	**2b**	a (100)[a]	155.4	−85.2	154.6	−107.8	156.8	−100.3
			b (0)[a]	180.7	−87.2	181.3	−106.3	183.4	−98.9
25	**1a**	**3a**	a (90)[a]	145.6	−156.5	149.1	−176.3	151.6	−163.2
			b (10)[a]	152.6	−171.7	155.4	−185.8	156.7	−178.4
26	**1a**	**3h**	a (24)[a]	140.9	−178.7	141.3	−189.7	145.8	−182.6
			b (76)[a]	137.2	−192.8	138.8	−208.7	138.9	−199.6
28	**1c**	**3b**	a (96)[a]	145.9	−141.5	144.5	−159.9	145.5	−150.4
			b (4)[a]	156.3	−149.4	163.0	−164.5	159.8	−157.8

[a] Predicted product ratio based on DFT calculations.

Table 4. Distortion energies, energies of interaction and activation energies (in kJ mol^{-1}) for selected triazoles calculated at B3LYP/6-311++G(2d,2p).

	R^1	R^2	Isomer	ΔE_d^+ (azide)	ΔE_d^+ (alkyne)	ΔE_d^+ (total)	ΔE^+	ΔE_i^+
6	**1a**	**2b**	a	92.0	34.3	126.3	100.5	−25.8
			b	89.6	53.1	142.7	125.2	−17.5
13	**1a**	**2i**	a	84.6	35.9	120.4	99.6	−20.8
			b	83.0	53.1	136.1	115.1	−21.0
14	**1c**	**2b**	a	88.8	35.1	123.9	100.5	−23.4
			b	90.1	52.2	142.3	125.3	−17.0
25	**1a**	**3a**	a	79.8	34.5	114.3	96.0	−18.3
			b	78.0	38.7	116.7	101.1	−15.6
26	**1a**	**3h**	a	75.3	33.7	109.1	88.3	−20.8
			b	70.8	31.6	102.4	84.6	−17.8
28	**1c**	**3b**	a	80.9	33.2	114.1	93.9	−20.3
			b	81.0	36.5	117.5	105.2	−12.3

Compared to Houk's investigations, the azide N-N-N angles of about 135° provide a hint for a late transition state of the corresponding 1,3-dipolar cycloaddition with silylated acetylene compounds.

Additionally, an analogous study was performed for the cycloaddition exhibiting the highest (triazole **14**) and a lower (triazole **13**) experimentally found 1,5-regioisomeric ratio. As expected, in both cases the 1,5-regiosiomeric favoritism was confirmed repeatedly (Table 3). In contrast to the synthetic experiment, the DFT-calculation of triazole **13** does reflect a marginal influence of an electron-withdrawing group in silylated acetylene derivates. For the consideration of water as solvent, solvent corrections were performed both by using the conductor-like polarizable continuum model C-PCM[25] and Truhlar and co-workers' SMD[26] solvation model, which is based on the quantum mechanical charge density of the solute molecule. However, solvent corrections for water with both models at B3LYP/6-311++G(2d,2p) level provided similar results compared to the gas-phase regioisomeric preference. Here, the computed stability of the triazole isomers depends on the model used. Nevertheless, the $\Delta\Delta G$ values are not significantly different. While the practical results showed that the silyl group has a dominant influence on the regioselectivity, it was decided to use a related DFT-model and solvent corrections of 1,3-dipolar cycloadditions with selected unsilylated acetylenes (triazoles **25**, **26**, and **28**). In the gas phase, the differences in the transition state energies are found to be less compared to the cycloaddition reactions with silylated acetylenes. For example, the activation energy of **26b(ts)** is computed to be 3.7 kJ mol^{-1} lower than that for **26a(ts)**. Evidently, these low energy differences in the activation barrier diminish the preference of regioselectivity. The gas phase findings of the calculated regioselectivities are in good agreement with the practical results, favoring the 1,4-addition for the triazole **26** and the 1,5-addition for the triazole **28**. Notwithstanding, in the case of triazole **25**, the examination of both transition states predicts a change of the regioselectivity. The calculations of solvent energy corrections of the studied triazoles in water are nearly equivalent (Table 3) compared to the gas phase.

Moreover, the activation barriers for these 1,3-dipolar cycloadditions were analyzed by using the distortion/interaction reactivity model for 1,3-dipolar cycloadditions developed by Houk and co-workers.[24] The distortion energy (ΔE_d^+) corresponds to the energy required for deforming the 1,3-dipole and the dipolarophiles into their transition state geometries, while the energy of interaction (ΔE_i^+) is derived from electrostatic and frontier orbital interactions (activation energy $\Delta E^+ = \Delta E_d^+ + \Delta E_i^+$). A comparison of

the distortion energies of the azides and acetylene compounds provides information about their reactivity (Table 4). The distortion energies for triazoles **6a,b** are computed to be 142.7 kJ mol^{-1} (**6b(ts)**) and 126.3 kJ mol^{-1} (**6a(ts)**), respectively, indicating an enhanced reactivity to form the 1,5-isomer. The decreased distortion energy is further reflected by a larger azide angle in the transition state geometry of **6b(ts)** (135.4°) compared to **6a(ts)** (134.7°) (Figure 3). As expected, the 1,5-isomer **6a(ts)** shows an additional increase of the stabilizing interaction energy (−25.8 kJ mol^{-1}) in comparison to the 1,4-isomer **6b(ts)** (−17.5 kJ mol^{-1}).

The distortion energies for the silylated triazoles **13** and **14** are very close to those for **6**. In both cases, the formation of the 1,5-isomer is preferred, which is predominantly reflected by lower total distortion energies. For example, the distortion energy of **14a(ts)** is 18.4 kJ mol^{-1} lower than that of the 1,4-isomer **14b(ts)**. The results obtained from the distortion/interaction model for the silylated triazoles **6**, **13**, and **14** are also in good agreement with the experimental data. Analogously, the differences in the total distortion energies of the unsilylated triazoles (**25**, **26**, and **28**) are less compared to the respective energies of the silylated triazoles, reflecting the dominant role of the silyl group in this kind of dipolar cycloaddition. The total distortion energy of **25a(ts)** is only 2.4 kJ mol^{-1} lower than that of **25b(ts)**. The favoritism regarding both regioisomers is similar and, owing to the uncertainties in the accuracy of the DFT functional used, nearly equal. Also, this finding is in agreement with the experimental results. Changing the phenyl moiety in the acetylene compound **3a** to an ester functionality, an increased participation of the 1,4-isomer was experimentally found (triazole **26**). The difference in the total distortion energies of **26b(ts)** and **26a(ts)** is calculated to be 6.7 kJ mol^{-1}, indicating a stronger preference of the 1,4-isomer compared to **25**. This result is in good accordance with the experiment. Finally, in order to elucidate the preference of the 1,5-regioisomer in the case of 1,3-dipolar cycloaddition of unsilylated acetylenes, the reaction between 3,4,5-trimethoxyphenylazide **1c** and mesitylacetylene **3b** was considered. The calculated distortion energies for **28a(ts)** and **28b(ts)** indicate only a slight preference of the 1,5-regioisomer. However, a difference of the energies of interaction of 8.0 kJ provides additional support for the high 1,5-regioisomeric privilege.

Conclusions

Simple and practical methods for the 1,5-regioselective azide–alkyne [3+2]-cycloaddition without heavy metal catalysis are rarely known in literature. The intent of this work was to focus on the use of substituted trimethylsilylacetylenes in order to induce regioselectivity. Inspired by the work of Hlasta and co-workers,[14] a fundamental investigation considering the performance of regioselective azide–alkyne cycloadditions by support of trimethylsilyl groups was targeted, since thermal dipolar cycloadditions of azides and alkynes are commonly known as being unselective in regio-orientation.[27] Water was used by default as dispersant in azide–alkyne cycloaddition because of its promising properties for cycloadditions[28] and for economic reasons. As a result, an efficient and highly regioselective metal-free synthesis route for substituted 1,2,3-triazoles by using a thermal dipolar cycloaddition reaction between readily and inexpensively accessible trimethylsilylacetylenes and azides in aqueous media was developed.

The results illustrate a high regiopreference induced by the trimethylsilyl moiety, with additional support for this tendency achieved through electron-releasing alkyne substituents. A comparable trend was observed with regard to the azide substituent. In contrast, electron withdrawing alkyne/azide substituents effect a marginal, but detectable decrease in regioselectivities.

In order to support these findings more sensitively, additional studies using the corresponding unsilylated terminal alkynes were examined. While the previous tendencies were confirmed, the regiodirective influence of the azide substituent turned out to be less potent than that of the alkyne substituent.

Accordingly, the highest 1,5-regiopreferences can be expected by using a TMS-alkyne and an azide, both attached to electron-releasing groups (see triazole **14a**). Additionally, the controlled TMS-cleavage of hydrolytically very stable silylated triazoles has been demonstrated.

DFT-calculations on selected reactions were performed to understand the influence of TMS-substituted acetylenes on the predominate regioselectivity. The calculated activation barriers showed that the differences between the regioisomeric paths are significant. The silylated acetylenes prefer 1,5-regiochemistry in the gas phase and, according to solvation models, the relative stabilities of the products barely differ. Extended calculations using the distortion/interaction model also confirmed the 1,5-regiochemistry. The total distortion energies to acquire the transition state geometries are lower compared to the 1,4-isomers and predict a higher reactivity to form the 1,5-regioisomer.

Finally, the trimethylsilyl induced 1,5-regioselective azide–alkyne cycloaddition has been shown to be a simple and powerful synthetic tool which provides convenient access to 1,5-disubstituted-4-(un-)silylated 1*H*-1,2,3-triazoles in high regioselectivities and good yields. Our protocol complements modern regioselective metal catalyzed azide–alkyne cycloaddition strategies and, thus, sets the stage for a variety of synthetic applications.

Experimental Section

General Methods

All reagents (e.g., **1b**, **2a**, **2c–f**, **2k**, **3a**, **3h**) were obtained from commercial suppliers and used without additional purification unless stated otherwise. Dry THF was obtained by a PS-MD-4-EN solvent purification system (Innovative Technologies Inc.). Diisopropylamine and triethylamine were dried over potassium hydroxide and were freshly distilled before use. Water was deionized by a Seralsoft SW 300 device with a Ser-

aDest SD2000 combined ion exchanger and used without further treatment. *Tetrakis*(triphenylphosphine)palladium(0)[29] was obtained according to literature procedures. Chromatographic separations were executed on silica gel (Kieselgel 60, 40–63 μm, Merck KGaA). Reaction progress was tracked by thin layer chromatography (TLC) (silica gel on aluminum sheets 20×20 cm with fluorescent dye (254 nm), Merck KGaA) or GC-MS. Regioselectivities were quantified by ^{1}H NMR spectroscopy of the dried crude products after qualitative analysis (GC-MS, TLC) and supported by GC-MS/FID measurements (ratio of peak areas). Yields were not optimized.

Instrumentation

All 1D (^{1}H, ^{13}C, and selective NOESY experiments) and 2D NMR (^{1}H-^{1}H COSY, HSQC, NOESY, HMBC) have been recorded in deuterated solvents (euriso-top) on a Bruker AVANCE 250, 300 or 400 MHz instrument. The chemical shifts are reported in ppm relative to the solvent residual peak (δ ($CHCl_3$) = 7.26 ppm, δ ($CHDCl_2$/CH_2Cl_2) = 5.32 ppm). Gas-chromatographic monitoring of the reaction progress was executed on a Shimadzu GC2010 equipped with ATAS GL-series OPTIC3 multipurpose injector and coupled with a Shimadzu GCMS-QP 2010S electron impact (EI) quadrupole mass spectrometer. Regioisomeric ratios were determined with a Thermo Trace GC simultaneously providing an FID (flame ionization detector) and a PolarisQ EI - ion trap mass spectrometer. Elemental analyses were obtained on a vario EL III Elementaranalysator (Analysensysteme GmbH Hanau). Melting points of solids were studied with a NAGEMA PHMK 05 hotplate microscope. Infrared spectra were recorded on a Bio-Rad FTS 25 or on a Nicolet Avatar 320 FT-IR by using the attenuated total reflectance (ATR) technique.

Crystal Structure Determination

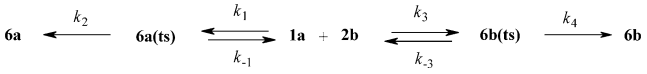
The intensity data for the compounds were collected on a Nonius Kappa CCD diffractometer, using graphite monochromated Mo-K_α irradiation. Data were corrected for Lorentz and polarization effects, but not for absorption effects.[30,31] The structures were solved by direct methods (SHELXS[33]) and refined by full-matrix least squares techniques against F_o^2 (SHELXS-97[33]). The absolute configuration of **11a** could be determined. The hydrogen atom for the hydroxy group of **23a** was located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[33] Crystallographic data as well as structure solution and refinement details are summarized in Table S1 (Supporting Information). XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations. CCDC 817830 (**8a**), 817831 (**9a**), 817832 (**11a**), 817833 (**13a**), 817834 (**14a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational Methods

Full geometry optimizations without symmetry constraints were carried out with the GAUSSIAN09[34] program package. All geometry optimizations reported herein were performed by using the well-established hybrid B3LYP[35] density functional method in combination with the 6–311++G(2d,2p)[36] basis set, which includes diffuse functions[37] on all atoms as well as 2 sets of d functions on heavy atoms supplemented by 2 sets of p functions on hydrogens.[38] All calculated stationary points were characterized as minima or transition structures on the potential hypersurface, according to the number of imaginary modes, by applying a second-order derivative calculation (vibrational analysis) at the same level of theory as that at which the optimization was performed. Vibrational analysis was also initiated to derive the ZPEs and thermochemical corrections for the enthalpies and free energies. All energies related to standard thermodynamics are given as enthalpies, however, kinetic descriptions of reaction paths are given as relative Gibbs free energies in relation to separated reactants. Solvent corrections were performed both by using the conductor-like polarizable continuum model C-PCM[25a] and Truhlar and co-workers' SMD[26] solvation model, which is based on the quantum mechanical charge density of the solute molecule. Water was used as solvent in respect of the experimental paragon. NBO analysis was achieved by using the Gaussian included NBO program.[39] The relative rate constants of competitive reactions are described by Eyring transition-state theory ([Eq. (1)].[40]

$$k_1/k_2 = e^{-\frac{\Delta G_1^{\ddagger} - \Delta G_2^{\ddagger}}{RT}} \quad (1)$$

The steady-state approximation results in Equations (2)–(3) derived from processes shown in Scheme 4. The product formation is deduced exemplary from **6a,b**.



Scheme 4. Schematic representation of the equilibrium.

$$k_1[\mathbf{1a}][\mathbf{2b}] = (k_{-1}+k_2)[\mathbf{6a}(\mathbf{ts})] \quad (2)$$

$$k_3[\mathbf{1a}][\mathbf{2b}] = (k_{-3}+k_4)[\mathbf{6b}(\mathbf{ts})] \quad (3)$$

Based on Equations (2)–(3), the formula of formation ratio on the example of the products **6a** and **6b** is given in Equation (4). All the rate constants were computed directly from Gibbs free energies according to Equation (1).

$$[\mathbf{6a}]/[\mathbf{6b}] = k_1k_2(k_{-3}+k_4)/k_3k_4(k_{-1}+k_2) \quad (4)$$

General Procedure for the Preparation of 1,2,3-Triazoles in Water[19]

A mixture of azide (1.0 eq.) and alkyne (1.0 eq.) was filled into a glass vessel for microwave applications (Biotage, 5 mL), equipped with a magnetic stirrer bar. Water was added to the solution (approximately 3 mL for 1 mmol of the azide, for more details, see Supporting Information) and the vial was closed with a crimp cap. The mixture was allowed to warm up by using a fitting aluminum heat exchanger on a magnetic stirrer equipped with a contact thermostat (80–120 °C). The resulting emulsion was stirred at the highest setting for several hours (see Supporting Information) and monitored by GC-MS. The vessel was cooled down to room temperature. The water was removed directly with a rotary evaporator. Subsequently, the residue was dried in fine vacuum and used without further purification for ^{1}H NMR spectroscopy and GC-MS/FID measurements to determine the ratio of the regioisomers. The remaining part was treated as described in the detailed substance information (Supporting Information).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201100404 containing preparation, substance characterization, NMR data, DFT results. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publications (see Supporting Information).

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[1] R. Huisgen, *Angew. Chem.* **1963**, *75*, 604–637; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598.

[2] a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; b) C. W. Tornøe, M. Meldal in *Peptides: The Wave of the Future* (Eds.: M. Lebl, R. A. Houghten), American Peptide Society, San Diego, **2001**, pp. 263–264; c) V. V. Rostovtsev, L. G. Green,

V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; d) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; e) C. Spiteri, J. E. Moses, *Angew. Chem.* **2010**, *122*, 33–36; *Angew. Chem. Int. Ed.* **2010**, *49*, 31–33.

[3] a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999; b) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930; c) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.* **2007**, *9*, 5337–5339.

[4] B. Liu, D Cui, *Dalton Trans.* **2009**, 550–556.

[5] A. Krasiński, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237–1240.

[6] a) M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Gerga, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, B. H. J. Yagi, *J. Med. Chem.* **2000**, *43*, 953–970; b) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185–4194; c) M. Whiting, J. C. Tripp, Y.-C. Lin, W. Lindstrom, A. J. Olson, J. H. Elder, K. B. Sharpless, V. V. Fokin, *J. Med. Chem.* **2006**, *49*, 7697–7710; d) D. R. Buckle, C. J. M. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem.* **1986**, *29*, 2262–2269.

[7] a) B. Schulze, C. Friebe, M. D. Hager, A. Winter, R. Hoogenboom, H. Görls, U. S. Schubert, *Dalton Trans.* **2009**, 787–794; b) B. Happ, C. Friebe, A. Winter, M. D. Hager, R. Hoogenboom, U. S. Schubert, *Chem. Asian J.* **2009**, *4*, 154–163; c) B. Beyer, C. Ulbricht D. Escudero, C. Friebe, A. Winter, L. Gonzalez, U. S. Schubert, *Organometallics* **2009**, *28*, 5478–5488; d) R. M. Meudtner, M. Ostermeier, R. Goddard, C. Limberg, S. Hecht, *Chem. Eur. J.* **2007**, *13*, 9834–9840; e) Y. J. Li, J. C. Huffman, A. H. Flood, *Chem. Commun.* **2007**, 2692–2694.

[8] C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem.* **2009**, *121*, 4998–5006; *Angew. Chem. Int. Ed.* **2009**, *48*, 4900–4908.

[9] a) E. M. Sletten, C. R. Bertozzi, *Org. Lett.* **2008**, *10*, 3097–3099; b) D. H. Ess, G. O. Jones, K. N. Houk, *Org. Lett.* **2008**, *10*, 1633–1636; c) S. T. Laughlin, J. M. Baskin, S. L. Amacher, C. R. Bertozzi, *Science* **2008**, *320*, 664–667; d) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272–1279.

[10] a) N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo, C. R. Bertozzi, *ACS Chem. Biol.* **2006**, *1*, 644–648; b) J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli, C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16793–16797.

[11] W. Kirmse, L Horner, *Liebigs Ann. Chem.* **1958**, *614*, 1–3.

[12] Z. Li, T. S. Seo, J. Ju, *Tetrahedron Lett.* **2004**, *45*, 3143–3146.

[13] a) L. Birkofer, A. Ritter, H. Uhlenbrauck, *Chem. Ber.* **1963**, *96*, 3280–3288; b) D. J. Hlasta, J. H. Ackerman, *J. Org. Chem.* **1994**, *59*, 6184–6189; c) S. Businelli, D. Di Martino, P. Zanirato, *Arkivoc* **2001**, (i), 131–143; d) K. W. Choi, M. A. Brimble, *Org. Biomol. Chem.* **2008**, *6*, 3518–3526.

[14] S. J. Coats, J. S. Link, D. Gauthier, D. J. Hlasta, *J. Org. Lett.* **2005**, *7*, 1469–1472.

[15] a) S. Mehta, R. C. Larock, *J. Org. Chem.* **2010**, *75*, 1652–1658; b) J. Huang, S. J. F. Macdonald, J. P. A. Harrity, *Chem. Commun.* **2009**, 436–438; c) J. Huang, S. J. F. Macdonald, A. W. J. Cooper, G. Fisher, J. P. A. Harrity, *Tetrahedron Lett.* **2009**, *50*, 5539–5541.

[16] a) J. W. Wijnen, S. Zavarise, J. B. F. N. Engberts, *J. Org. Chem.* **1996**, *61*, 2001–2005; b) S. Otto, W. Blokzijl, J. B. F. N. Engberts, *J. Org. Chem.* **1994**, *59*, 5372–5376; c) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772.

[17] S. Thorand, N. Krause, *J. Org. Chem.* **1998**, *63*, 8551–8553.

[18] H. Hu, A. Zhang, L. Ding, X. Lei, L. Zhang, *Molecules* **2008**, *13*, 556–566.

[19] Z.-X. Wang, H.-L. Qin, *Chem. Commun.* **2003**, 2450–2451.

[20] P. Zanirato, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2789–2796.

[21] S. Hiraoka, K. Hirata, M. Shionoya, *Angew. Chem.* **2004**, *116*, 3902–3906; *Angew. Chem. Int. Ed.* **2004**, *43*, 3814–3818.

[22] J. A. Demaray, J. E. Thuener, M. N. Dawson, S. J. Sucheck, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4868–4871.

[23] F. Schoenebeck, D. H. Ess, G. O. Jones, *J. Am. Chem. Soc.* **2009**, *131*, 8121–8133.

[24] a) D. H. Ess, K. N. Houk, *J. Am. Chem. Soc.* **2007**, *129*, 10646–10647; b) D. H. Ess, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 10187–10198.

[25] a) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995–2001; b) M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comput. Chem.* **2003**, *24* 669–681.

[26] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

[27] M. V. Gil, M. J. Arévalo, Ó. López, *Synthesis* **2007**, 1589–1620.

[28] D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.

[29] D. R. Coulson, *Inorg. Chem.* **1972**, *13*, 121.

[30] COLLECT, Data Collection Software; B. V. Nonius, Netherlands, **1998**.

[31] Z. Otwinowski, W. Minor in *Methods in Enzymology, Macromolecular Crystallography Part A*, *Vol. 276* (Eds: C. W. Carter, R. M. Sweet), Academic Press, **1997**, pp. 307–326.

[32] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112–122.

[33] G. M. Sheldrick, SHELXL-97 (Release 97–2), Göttingen University, Germany, **1997**.

[34] Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H Nakai, T Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[35] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.

[36] a) R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650; b) A. D. McLean, G. S. Chandler, *J. Chem. Phys.* **1980**, *72*, 5639–5648.

[37] T. Clark, J. Chandrasekhar, G. W. Spitznagel, P. v. R. Schleyer, *J. Comput. Chem.* **1983**, *4*, 294–301.

[38] M. J. Frisch, J. A. Pople, J. S. Binkley, *J. Chem. Phys.* **1984**, *80*, 3265–3269.

[39] NBO Version 3.1, E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold.

[40] a) H. Eyring, *J. Chem. Phys.* **1935**, *3*, 107; b) J. Keith, M. Laidler, C. King, *J. Phys. Chem.* **1983**, *87*, 2657–2664.

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