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Nickel-Catalyzed Azide–Alkyne Cycloaddition to Access 1,5-Disubstituted 1,2,3-Triazoles in Air and Water

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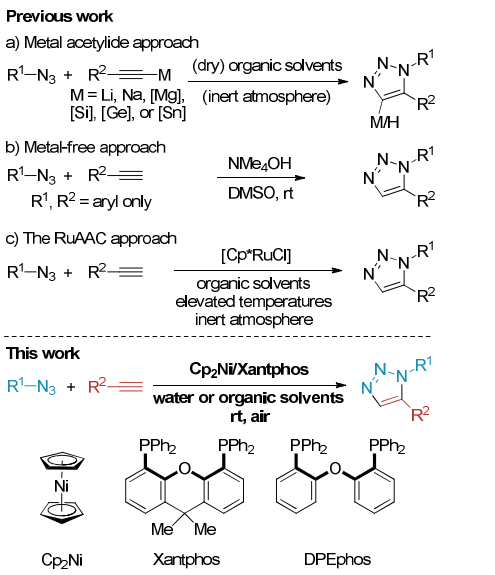
Supporting Information Placeholder

ABSTRACT: Transition-metal-catalyzed or metal-free azide–alkyne cycloadditions are versatile and indispensable synthetic methods to access 1,4- or 1,5-disubstituted 1,2,3-triazoles. Although the copper-catalyzed cycloaddition to access 1,4-disubstituted products has been successfully applied to biomolecular reaction systems, the azide–alkyne cycloaddition to access the complementary 1,5-regioisomers under aqueous and ambient conditions remains a formidable challenge due to limited substrate scope or moisture-/air-sensitive catalysts. Herein, we report a general synthetic method to access 1,5-disubstituted 1,2,3-triazoles using a Cp_2Ni/Xantphos catalytic system. The reaction proceeds both in water and organic solvents at room temperature. This protocol is operationally simple and scalable with a broad substrate scope including both aliphatic and aromatic substrates. Moreover, triazoles attached with carbohydrates or amino acids are readily prepared via this nickel-catalyzed azide–alkyne cycloaddition.

Switching the regiochemical outcome is one of the critical issues in modular synthetic approaches involving carbon–heteroatom bond-forming processes.[1] It is particularly important to impart a high level of regiocontrol to the Huisgen 1,3-dipolar cycloaddition, which directly assembles two molecular bricks, an organic azide and an alkyne, with ideal atom economy.[1,2] The thermal cycloaddition exhibits high activation barriers and poor regioselectivity at elevated temperatures. Rapid and regioselective formation of 1,4-disubstituted products has been accomplished by the copper-catalyzed azide–alkyne cycloaddition (CuAAC), since the first independent reports by the groups of Sharpless and Meldal.[3] The main features of this widely utilized click chemistry include operational simplicity, mild conditions, a broad substrate scope, bioorthogonality, favorable kinetics, and high yields. The transformation proceeds not only in organic solvents, but also in aqueous media at room temperature. As the 1,4-disubstituted 1,2,3-triazole scaffold is chemically stable, aromatic, and pharmacologically important, the CuAAC reactions have flourished in medicinal chemistry, materials science, and chemical biology.[1,2,4]

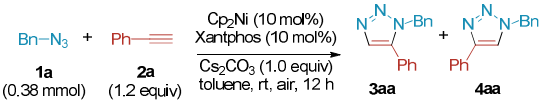
Scheme 1. Synthesis of 1,5-Disubsituted 1,2,3-Triazoles



Synthetic pathways complementary to the CuAAC have been developed to access 1,5-disubstituted 1,2,3-triazoles. As illustrated in Scheme 1a, a metal acetylide reacts with an organic azide to afford a 4-metalated triazole.[5] Subsequent aqueous quenching can lead to product formation.[5a,5c,5d] Kwok *et al.* introduced a metal-free synthetic route to furnish 1,5-diaryl-1,2,3-triazoles (Scheme 1b).[6] Fokin, Jia, and co-workers reported the ruthenium-catalyzed azide–alkyne cycloaddition (RuAAC), obtaining a range of desired products under inert atmosphere (Scheme 1c).[7] However, the

RuAAC reactions using [Cp*RuCl] complexes are typically sensitive to water and air, and proceed at elevated temperatures.[8] These conditions limit their application in biochemical research. Pertinent to these precedents, the development of convenient synthetic methods compatible with aqueous and ambient conditions remains a formidable challenge.[9] Herein we report a general synthetic strategy to access 1,5-disubstituted 1,2,3-triazoles by the nickel-catalysis. Notably, functionalization of carbohydrates and amino acids has been also accomplished via this newly developed nickel-catalyzed azide–alkyne cycloaddition (NiAAC) in water at room temperature.

Table 1. Optimization of Reaction Conditions[a]

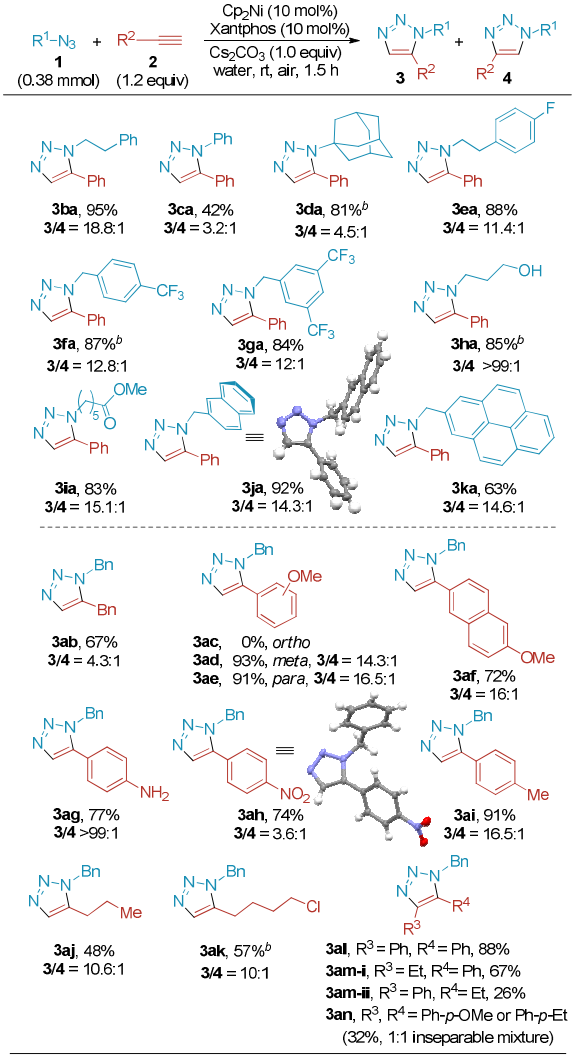


entry	change from above conditions	yield [%][b]	
		3aa	**4aa**
1	None	94	6
2	no Cp_2Ni	0	0
3	$NiCl_2{\cdot}6H_2O$ (instead of Cp_2Ni)	0	0
4	Cp_2Ru (instead of Cp_2Ni)	0	0
5	no Xantphos	0	0
6	DPEphos (instead of Xantphos)	76	9
7	no Cs_2CO_3	70	10
8	Cp_2Ni (5 mol%)/Xantphos (5 mol%)	38	4
9	75 °C	55	5
10	100 °C	70	9
11	1.5 h	91	6
12	DMF (instead of toluene)	90	8
13	DCM (instead of toluene)	90	3
14	**water (instead of toluene), 1.5 h**	**91**	**6**

[a]Reaction conditions: **1a** (0.38 mmol), **2a** (0.46 mmol, 1.2 equiv), Cp_2Ni (10 mol%), Xantphos (10 mol%), Cs_2CO_3 (1.0 equiv) in toluene (2.0 mL) at rt under air for 12 h. [b]Isolated yield. Bn, benzyl; Cp, cyclopentadienyl.

We initiated our investigation of the NiAAC by treating two simple substrates, benzyl azide **1a** and phenyl acetylene **2a**, with a catalytic amount of nickel precatalyst at room temperature without any efforts to exclude air and moisture (Table 1). All reagents including precatalysts, ligands, and solvents were used as-received from standard suppliers with no extra purification steps. After extensive screening of precatalysts, ligands, and additives (see the Supporting Information, Tables S1–S4), the reaction conditions were optimized to achieve high yield and excellent regioselectivity. Under the standard conditions, the desired 1,5-disubstituted triazole **3aa** was isolated in 94% yield with only 6% of **4aa** (entry 1). The regioisomers were readily separated by flash column chromatography. In the absence of the nickelocene (Cp_2Ni) precatalyst or the bidentate Xantphos ligand, the 1,2,3-triazole core was not formed (entries 2–5). Control experiments showed that nickel precatalysts lacking the Cp ligands or other metallocene complexes were ineffective (entries 2–4; see the Supporting Information, Tables S1 and S2). Yet, more sterically demanding Cp-based complexes resulted in comparable or unsatisfactory results (Table S2). Replacement of Xantphos with other P- or N-ligands caused diminished or no catalytic activity (Table S3). The use of DPEphos as the ligand, which has a similar structure to Xantphos (Table 1, entry 6; see also Scheme 1), furnished **3aa** in 76% yield. Geometrical constraints such as the rigidity of the backbone and a wide bite angle may play a critical role in determining the reactivity of the NiAAC.[10] Among the mild bases screened, Cs_2CO_3 was optimal (Supporting Information, Table S4). The reaction was less effective when the precatalyst/ligand loading was reduced (Table 1, entry 8). Elevated temperatures (entries 9 and 10) lowered the reaction yield and regioselectivity, presumably due to catalyst decomposition or the involvement of the thermal pathway. A shortened reaction time (1.5 h) did not significantly affect the yield (entry 11). The reaction proceeded well in other solvents including DMF, DCM, and even water (entries 12–14) with similar yields and regioselectivity. Intriguingly, this NiAAC reaction is highly compatible with water as the sole solvent and can be carried out under air at room temperature.

Scheme 2. Substrate Scope of the NiAAC[a]

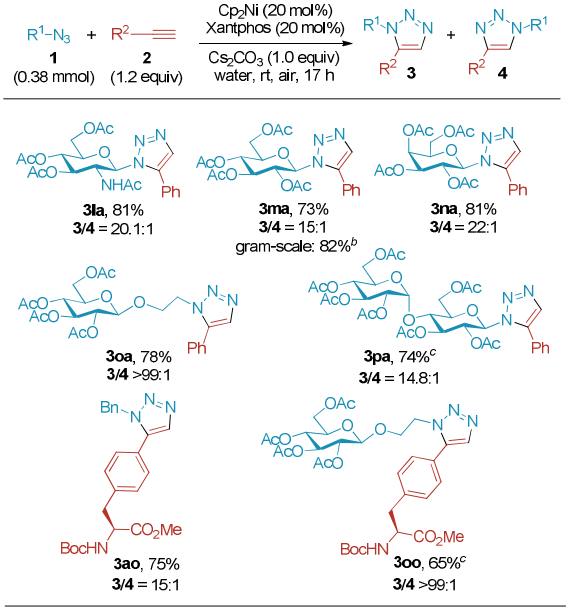


[a]Reaction conditions: **1** (0.38 mmol), **2** (0.46 mmol, 1.2 equiv), Cp_2Ni (10 mol%), Xantphos (10 mol%), Cs_2CO_3 (1.0 equiv) in water (2.0 mL) at rt under air for 1.5 h. Isolated yields of 1,5-products. [b]12 h.

With the optimized conditions based on the Cp_2Ni/Xantphos catalytic system in hand, the substrate scope and generality of this NiAAC reaction were investigated under aqueous conditions at room temperature (Scheme 2). Owing to the poor solubilities of the precatalyst, ligand, and substrates in water, the reactions were conducted as aqueous suspensions. The reactions of various azides (**1b** and **1e**–**1k**) produced the corresponding 1,5-disubstituted triazoles in moderate to excellent isolated yields (63–95%) with high regioselectivity ranging from 11.4:1 to >99:1 for **3**/**4**. However, the regioselectivity was significantly decreased when phenyl azide **1c** (3.2:1 ratio) or 1-azidoadamantane **1d** was used (4.5:1 ratio). This can be attributed to the steric congestion between the substrates and catalytic Ni species containing Cp and Xantphos ligands. Various functional groups of **1**, including fluorinated arenes and fused cyclic moieties, were compatible with the reaction conditions. In particular, the hydroxyl and ester functional groups remained intact during the catalysis, as illustrated in the cases of **3ha** and **3ia**.

Regarding the organic alkyne partner **2**, aliphatic and aromatic alkynes with diverse functional groups, including methoxy-, amine-, nitro-, chloro-, and methyl moieties, were well-tolerated. Yet, *ortho*-OMe-substituted alkyne **2c** showed no reactivity owing to the steric effect. The NiAAC reaction is strongly favored with less-sterically hindered *meta*- and *para*-substituted substrates **2d** and **2e**. It has been previously reported that the RuAAC reactions are significantly affected by the steric factor of alkynes.[7b] However, the contribution of electronic factor cannot be ruled out (**3ab**, **3ag**, and **3ah**). The cycloaddition of the electronically unbiased internal alkyne **2l** afforded **3al** in 88% yield. Unsymmetrical internal alkynes **2m** and **2n** also participated in the NiAAC to give fully-substituted triazoles,[7,8,11] albeit with poor regioselectivity. The regiochemical assignments were confirmed by 2D NMR spectra (Supporting Information, Section V),[3,8b,11] assisted by the ^{13}C chemical shifts of the triazole CH.[12] In addition, single-crystal X-ray crystallographic analyses unambiguously determined the structures of the 1,5-disubstituted triazoles **3ja** and **3ah** (Supporting Information, Section VI).

Scheme 3. Expanded Scope with Respect to Non-natural Carbohydrates and Amino Acids[a]



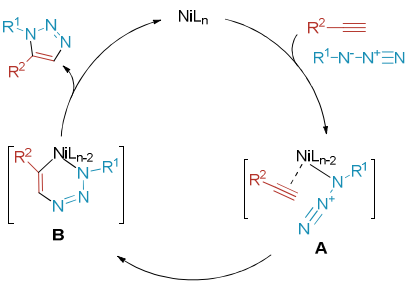
[a]Reaction conditions: **1** (0.38 mmol), **2** (0.46 mmol, 1.2 equiv), Cp_2Ni (20 mol%), Xantphos (20 mol%), Cs_2CO_3 (1.0 equiv) in water (2.0 mL) at rt under air for 17 h. Isolated yields of 1,5-products. [b]**1m** (1.0 g, 2.68 mmol). [c]**1** (0.19 mmol), 12 h in DCM.

To expand the repertoire of the NiAAC, this newly developed click reaction was explored to include biomolecules such as carbohydrates and amino acids. In particular, glycoconjugates feature unparalleled branched structures, compared with oligopeptides or oligonucleotides, with diverse configurations and glycosidic linkages.[4a,13] Their effective functionalization has been achieved by producing non-natural glycoconjugates and amino acid derivatives. Both *O*- and *N*-linked sugars were well-tolerated in this NiAAC (**3la**–**3oa**). In addition, the cycloaddition reaction could be scaled up to a 1 gram of **1m** with an increased reaction yield of 82% (**3ma**). Remarkably maltose azide **1p**, a disaccharide moiety, could be incorporated affording the cycloaddition product in 74% yield, albeit in DCM, due to the solubility problem. Finally, both carbohydrate **1o** and amino acid **2o** were subjected to the NiAAC, and non-natural glycoamino acid **3oo** was successfully prepared in 65% yield, presenting the potential of biomolecule conjugation. However, the attempted NiAAC reactions with unprotected sugars were not successful (see the Supporting Information, Section III-5).

Having established the utility of the Cp_2Ni/Xantphos catalytic system for azide–alkyne cycloaddition, we turned our attention to the Ni species that may be present in solution. Literature reports indicate that reaction of Cp_2Ni with mono- and bidentate phosphine ligands may, in some cases, give CpNi(P-ligand)$_2$ and Ni(P-ligand)$_4$ complexes.[14,15] The formal one-electron reduction steps of the Ni center (from Ni^{II} to Ni^{I} to Ni^{0}) upon coordination of the phosphine ligands may be explained by successive dissociation of $Cp^{\bullet}$ radicals.[16,17] Indeed, the analysis of the reaction between Cp_2Ni and Xantphos by EPR spectroscopy and mass spectrometry gave results consistent with the presence of CpNi(Xantphos) and Ni(Xantphos)$_2$ (see the Supporting Information, Section VII). The EPR spectrum of the reaction mixture shows a triplet resonance signal centered at $g = 2.088$ with a hyperfine splitting constant of $a = 104$ G (Figure S26), as expected for a paramagnetic Ni^{I} center ($S = 1/2$) coupled to two ^{31}P nuclei.[14,16–18] Moreover, these parameters are similar to those reported for related Ni complexes, such as CpNi(dppe).[14,16]

Next, the high-resolution ESI mass spectrum (Supporting Information, Section VII-2, Figure S27) of the reaction mixture exhibits the most-abundant peak at m/z 701.1671, which is attributed to $[CpNi(Xantphos)]^+$. Measured and calculated isotope distributions were well-matched. In addition, a peak at *m/z* 630.1638 is assigned to $[Ni(Xantphos)_2+2Na]^{2+}$.[15] Because the reactions in this study were performed under air, it may seem likely that CpNi(Xantphos), at least in part, undergoes oxidization, giving rise to the corresponding Ni^{II} complex $[CpNi(Xantphos)]^+$ detected in positive ESI mode. Taken together, this preliminary investigation agrees with the reaction sequences (i) $Cp_2Ni \rightarrow [CpNi(Xantphos)] \rightarrow [Ni(Xantphos)_2]$ and (ii) $[CpNi(Xantphos)] \rightarrow [CpNi(Xantphos)]^+$. More detailed studies are needed, however, to confirm the presence of these species and to determine which ones are involved in the NiAAC reaction.

Scheme 4. Tentative Reaction Mechanism of the NiAAC



Based on previous literature reports[19] and our experimental results, a tentative reaction mechanism is suggested as shown in Scheme 4. Alkyne and azide coordinate to Ni, forming intermediate **A**, while the spectator ligands (Cp and/or Xantphos) may change their bonding modes to accommodate the new ligands. Because both internal and terminal alkynes participate in this cycloaddition (*vide supra*, see Scheme 2), the formation of a nickel-acetylide species is excluded. The C–N bond formation between alkyne and azide giving complex **B** determines 1,5-regioselectivity, analogous to the RuAAC pathway.[7b] Subsequent reductive elimination leads to the formation of cyclized target product **3**, while regenerating NiL_n through association (or change of bonding mode) of the spectator ligands.

In summary, we have developed the nickel-catalyzed azide–alkyne cycloaddition to access 1,5-disubstituted 1,2,3-triazoles from readily available substrates and inexpensive reagents at room temperature. The Cp_2Ni precatalyst and Xantphos ligand were critical to accomplish the catalytic manifold, insensitive to molecular oxygen and water. This methodology exhibits a broad substrate scope, good functional group tolerance, high yields, and high regioselectivity, complementing the classical copper-catalyzed click chemistry that produces 1,4-disubstituted 1,2,3-triazoles. The synthetic utility of this nickel-catalyzed pathway has been highlighted by the functionalization of carbohydrates and amino acids. Further mechanistic studies of catalyst activation and intermediate formation are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Detailed experimental procedures, HRMS-ESI data, and NMR (^{1}H, ^{13}C, ^{19}F, NOESY, and HSQC) spectra (DOCX)
Single crystal X-ray data for **3ah** and **3ja** (CIF)

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Notes

The authors declare no competing financial interests.

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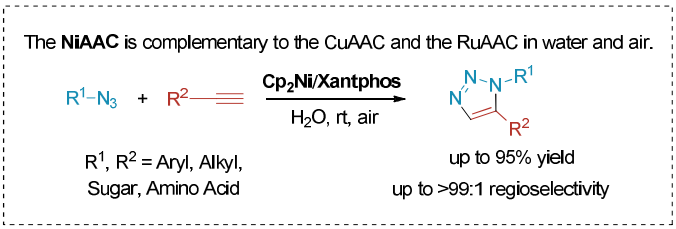
The NiAAC is complementary to the CuAAC and the RuAAC in water and air.
R1–N3 + R2
Cp2Ni/Xantphos
H2O, rt, air
R1, R2 = Aryl, Alkyl, Sugar, Amino Acid
up to 95% yield
up to >99:1 regioselectivity