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Zinc Triflate Catalyzed Aerobic Cross-Dehydrogenative Coupling (CDC) of Alkynes with Nitrones: A New Entry to Isoxazoles

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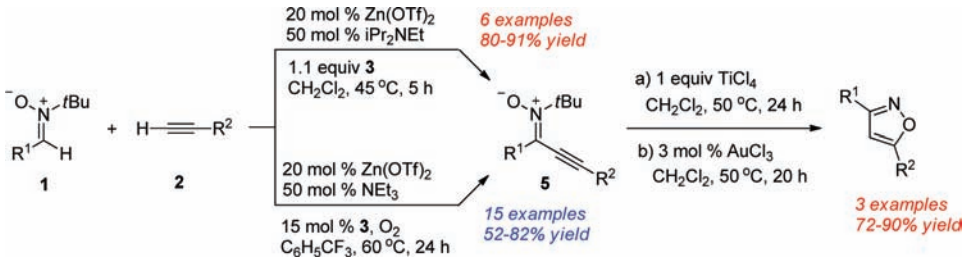
ABSTRACT



A mild, operationally simple cross-dehydrogenative coupling between nitrones and terminal alkynes is described by using cheap, readily available 3,3′,5,5′-tetra-*tert*-butyldipheno-quinone and dioxygen as oxidants. These cross-couplings can be performed on various nitrones and alkynes with good to excellent yields. Product nitrones are readily transformed to pharmaceutically important 3,5-disubstituted isoxazoles.

Development of selective and efficient C−C bond forming reactions is of paramount importance for organic chemistry. Transition-metal-catalyzed cross-coupling reactions using two prefunctionalized substrates belong to the most powerful processes for C−C bond formation.[1] Recently, transition-metal-catalyzed C−H bond activation with subsequent C−C bond formation has gained great attention.[2] However, in these cases one coupling partner still has to be prefunctionalized. Cross-dehydrogenative coupling (CDC) has emerged as a more atom economic approach for the construction of C−C bonds under oxidative conditions starting without prefunctionalized substrates.[3] Formally, two different C−H bonds are directly connected to the corresponding C−C bond under liberation of H_2. In recent years, some excellent pioneering studies have been published along this line.[3−6]

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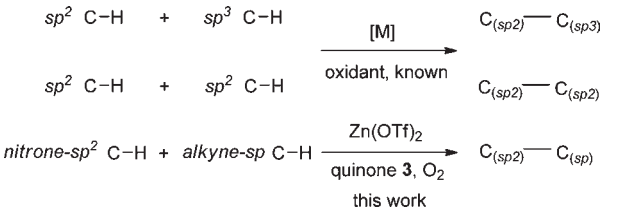
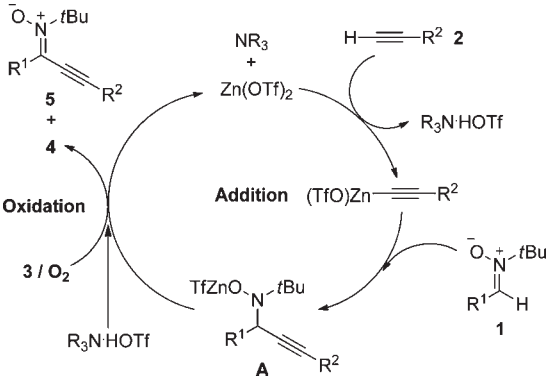
There are several reports on CDC processes comprising sp^2(C−H)/sp^3(C−H),[4d,5c,5i,5k] sp^2(C−H)/sp^2-(C−H),[4c,5b,5g,5h,5l−5n] and sp(C−H)/sp(C−H)[4e] couplings (Scheme 1). However, there are very few reports on successful sp^2(C−H)/sp(C−H) CDC reactions.[6] Herein, we disclose the first examples of zinc triflate catalyzed CDC reactions between sp^2(C−H) of nitrones and sp(C−H) of terminal alkynes in the presence of 3,3′,5,5′-tetra-*tert*-butyldipheno-quinone **3**[7] and dioxygen as oxidants for the preparation of alkynylated nitrones **5** (Scheme 1). Moreover, we will show that such nitrones are readily transformed to the corresponding isoxazoles.

Scheme 1. C−C Bond Formation via Cross-Dehydrogenative Coupling



C−C bond formation via reaction of a metalated terminal alkyne[8] with an electrophile is a classical approach for alkynylation. Products obtained are amenable to further synthetic transformations.[9] Transition-metal-catalyzed addition of alkynes to C=N bonds has been intensively studied.[10,11] Carreira's Zn(II)-catalyzed alkynylation of nitrones to propargyl *N*-hydroxylamines has caught our attention.[11a] We envisioned oxidizing propargyl *N*-hydroxylamine[12] intermediates of type **A** to the α-alkynylated nitrones **5**, while avoiding oxidative homocoupling of the metalated alkyne (Scheme 2). Hence, the oxidant must be compatible with the organozinc species. Our proposed cascade comprises a $Zn(OTf)_2/NR_3$ catalyzed nucleophilic addition of a terminal alkyne to an *N*-*t*Bu nitrone to **A**, followed by mild oxidation of **A** to the cross-dehydrogenatively coupled α-alkynylated nitrone **5**.

Scheme 2. Working Model for the CDC between *N*-*t*Bu Nitrones and Terminal Alkynes



The reason behind choosing the *t*Bu group as an *N*-substituent in the starting nitrones is 3-fold: (a) preliminary studies revealed that oxidation is fast for *N*-*t*Bu-substituted hydroxylamines, (b) oxidation occurs regioselectively,[13] and (c) the *t*Bu group is an established acid-sensitive protecting group. We started our studies by reacting isopropyl *N*-*t*Bu nitrone **1a** with alkyne **2a** (3 equiv) in the presence of $Zn(OTf)_2$ (20 mol %) and NEt_3 (50 mol %) in DCM at 45 °C. Various organic oxidants were employed for the initial screenings. No reaction was observed using DDQ (1 equiv), but the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical[14] (TEMPO, 2 equiv) delivered the desired **5a** in 74% yield (Table 1, entries 1, 2). The yield was improved to 84% with the readily available diquinone **3** as an oxidant (entry 3). Importantly, **3** can be regenerated from byproduct **4**.[7] Replacing iPr_2NEt with Et_3N gave a slightly lower yield (77%), which was improved to 83% by stirring the reaction mixture at rt, albeit at the expense of a longer reaction time (entries 4, 5). Hence, the optimal oxidant and base in terms of yield and reaction time were found to be diquinone **3** and iPr_2NEt.

We then tested the scope of our CDC under the optimized conditions. The (6-methoxy-2-naphthyl)alkynyl Zn compound underwent smooth transformation to **5e** in high

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(13) Under identical conditions using 2.2 equiv of TEMPO isopropyl *N*-Bn nitrone gave the desired product in 76% yield along with the undesired regioisomer formed via oxidation at the benzylic position in 9% yield.

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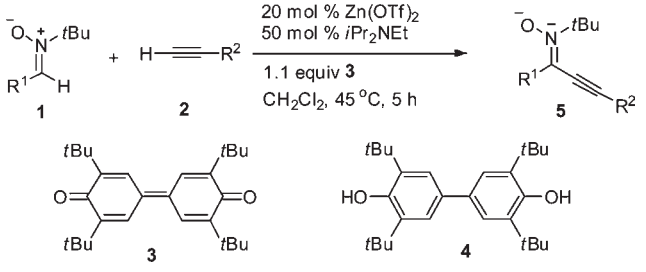
yield (entry 4). Terminal alkynes bearing sterically demanding aliphatic substituents (Me_3Si and *t*Bu) reacted with **1a** to give **5i, j** in high yields (entries 5,6). The nitrone substituent R^1 could also be varied (see **5k**, **5l**, entries 7, 8).

Table 1. CDC between Various Nitrones **1** and Alkynes **2** Using a Stoichiometric Amount of Oxidant **3**



entry	**1** (R^1)	**2** (R^2)	product	yield (%)[a]
1	Me_2CH	Ph	**5a**	n.r.[b]
2	Me_2CH	Ph	**5a**	74%[c]
3	Me_2CH	Ph	**5a**	84
4	Me_2CH	Ph	**5a**	77[d]
5	Me_2CH	Ph	**5a**	83[e]
6	Me_2CH	6-MeO-2-naphthyl	**5e**	87
7	Me_2CH	Me_3Si	**5i**	85
8	Me_2CH	*t*Bu	**5j**	80
9	c-C_6H_{11}	Ph	**5k**	87
10	c-C_5H_9	Ph	**5l**	91

[a] Yield of isolated product. [b] 1.1 equiv of DDQ was used as an oxidant. [c] 2.2 equiv of TEMPO were used as an oxidant. [d] NEt_3 used as a base. [e] At room temperature for 24 h using NEt_3 as a base.

We next envisioned running our CDC reaction catalytic in oxidant **3** in the presence of O_2 and began our studies by reacting **1a** with **2a** in the presence of 20 mol % $Zn(OTf)_2$, 50 mol % Hünig's base, 20 mol % of oxidant **3**, and dioxygen (1 atm, balloon, Table 2). Several solvents including DCM, THF, and DCE were screened. As compared to the stoichiometric protocol, **5a** was isolated in lower yields using DCM or THF, due to incomplete oxidation (entries 1, 2). An increase of the temperature by switching to DCE improved the yield to 59%; however, the product partly decomposed (entry 3). As fluorinated solvents do better dissolve dioxygen, we tested α,α,α-trifluorotoluene (BTF)[15]and the yield was improved to 72% at 60 °C (entry 6). Lower yields due to product decomposition were obtained at higher temperatures (entries 4, 5). Changing the loading of **3** to 15, 10, and 30 mol % did not affect the yield to a large extent (entries 7−9), and the highest yield was obtained with 40 mol % of **3** (80%, entry 10). CDC with O_2 in the absence of **3** gave **5a** in 55% yield (entry 11). These results indicate that back ground aerobic oxidation is occurring at a reasonable rate and regeneration of **3** from **4** with O_2 is not very efficient. However, the presence of **3** clearly leads to faster and cleaner reactions with higher yields. Decreasing the $Zn(OTf)_2$ loading led to worse results (entries 12−14), and switching to Et_3N as a base further improved the yield (76%, entry 13). The optimal loading of cooxidant **3** in terms of economy, yield, and reaction time was found to be 15 mol % (entries 8, 11, 15−17).

Table 2. CDC between Nitrone **1a** and Alkyne **2a** under Different Conditions Using Dioxygen and **3** as a Cooxidant

entry	[Zn] (mol %)	iPr_2NEt (mol %)	**3** (mol %)	solv/*t* (°C)	yield (%)[b]
1	20	50	20	DCM/40	28[c]
2	20	50	20	THF/66	46[c]
3	20	50	20	DCE/84	59[d]
4	20	50	20	BTF/100	45[d]
5	20	50	20	BTF/75	68[d]
6	20	50	20	BTF/60	72[e]
7	20	50	15	BTF/60	71
8	20	50	10	BTF/60	70[f]
9	20	50	30	BTF/60	74[g]
10	20	50	40	BTF/60	80[h]
11	20	50	–	BTF/60	55[i]
12	10	25	20	BTF/60	12[j]
13	15	40	20	BTF/60	66
14	15	40	10	DCE/60	46[c,j]
15	20	50[a]	15	BTF/60	76
16	20	50[a]	10	BTF/60	74[f]
17	20	50[a]	–	BTF/60	54[i]

[a] With NEt_3 as a base. [b] Yield of isolated product; reactions were carried out on a 0.5 mmol scale for 24 h. [c] Oxidation did not go to completion. [d] Decomposition was observed. [e] Reaction was finished in 20 h. [f] Reaction time extended to 30 h. [g] Reaction was finished in 18 h. [h] Reaction was finished in 16 h. [i] Reaction was carried out in absence of oxidant. [j] Addition did not go to completion.

Under optimized conditions reaction scope was explored (Table 3). Arylacetylenes bearing electron-donating and -withdrawing substituents at the aryl moiety reacted with **1a** to give **5b**−**e** with very good yields (entries 2−5). The bisalkyne homocoupling products were not identified. Enynes were observed to be good substrates (entry 6), and aliphatic terminal alkynes afforded **5g**,**h**,**j** in acceptable yields (entries 7, 8, and 10). Silyl protected alkyne underwent smooth transformation to **5i** (entry 9).

A wide range of nitrones **1** were then tested using phenylacetylene as a reaction partner. Aliphatic nitrones derived from cyclic aldehydes provided **5k**,**l**,**n** in good yields (entries 11, 12, and 14). Nitrones derived from acyclic aldehydes also worked well (entries 13, 15). Aromatic nitrones either worked sluggishly or did not react at all (results not shown).[11a]

Isoxazoles belong to an important class of five-membered nitrogen heterocycles that are embedded in a number of pharmaceutically important compounds.[16] Various methods for their preparation have been reported; however, only a few of them are general, regioselective, and

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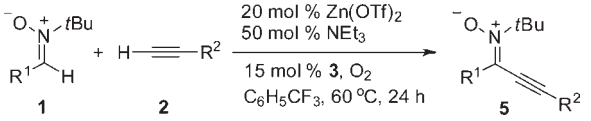
Table 3. CDC between Various Nitrones **1** and Alkynes **2** Using Oxidant **3** (15 mol %) and Dioxygen As Oxidants



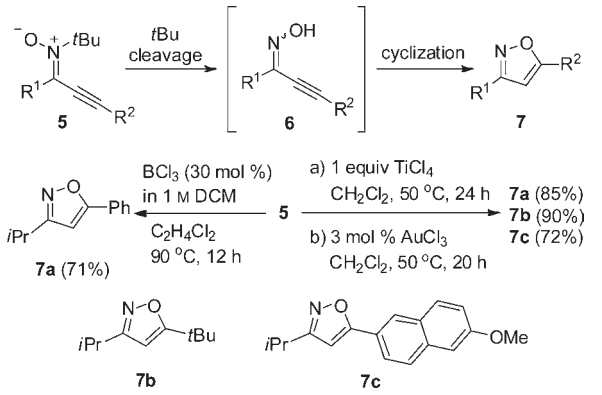
entry	**1** (R^1)	**2** (R^2)	product	yield (%)[a]
1	Me_2CH	Ph	**5a**	76
2	Me_2CH	3-Me-C_6H_4	**5b**	82
3	Me_2CH	4-MeO-C_6H_4	**5c**	72
4	Me_2CH	4-CF_3–C_6H_4	**5d**	77
5	Me_2CH	6-MeO-2-naphthyl	**5e**	80
6	Me_2CH	1-Cyclohex-1-enyl	**5f**	65
7	Me_2CH	*n*Pr	**5g**	67
8	Me_2CH	c-C_6H_{11}	**5h**	52
9	Me_2CH	Me_3Si	**5i**	68
10	Me_2CH	*t*Bu	**5j**	70
11	c-C_6H_{11}	Ph	**5k**	82
12	c-C_5H_9	Ph	**5l**	74
13	1-Phenylethyl	Ph	**5m**	65 (76)[b]
14	c-C_3H_5	Ph	**5n**	64
15	$C_6H_5CH_2CH_2$	Ph	**5o**	62

[a] Yield of isolated product and reactions were carried out on a 0.5 mmol scale. [b] Yield in the bracket obtained with 30 mol % $Zn(OTf)_2$ and 60 mol % of NEt_3.

high yielding.[17–19] The [3 + 2] cycloaddition of alkynes with nitrile oxides, which probably belongs to the most direct route to isoxazoles, shows some drawbacks such as competing dimerization of the nitrile oxides, low yields, and occasional lack of regioselectivity.[20] We thought that selective removal of the *N*-*t*Bu group of the CDC products **5** should deliver oximes **6**, which should undergo cyclization to give 3,5-disubstituted isoxazoles **7** (Scheme 3).

We first tested various Brønsted and Lewis acids under different conditions for the direct transformation of **5a** to isoxazole **7a**. Unfortunately, most of them either failed to react (scandium tiflate, ytterbium triflate, copper triflate, tin triflate) or provided multiple products (conc. HCl, HCl in dioxane, HCl in methanol, HCl in isopropanol, triflic acid, trifluoroacetic acid). In some cases **7a** was obtained in a poor yield along with **5a** (BF_3/Et_2O, BBr_3). However, BCl_3 (30 mol %) in dichloroethane at 90 °C provided **7a** in a good yield (71%). We also found that **5a** undergoes quantitative cleavage of the *t*Bu group to give oxime **6a** with $TiCl_4$ in CH_2Cl_2 (sealed tube at 50 °C for 24 h). Gold-catalyzed cycloisomerization[18,21] of **6a** eventually afforded **7a** in 85% overall yield. The two-step protocol was also successfully applied to the preparation of **7b** and **7c**.

Scheme 3. Transformation of Alkynylnitrones **5** to 3,5-Disubstituted Isoxazoles **7**



In conclusion, we have documented an efficient zinc triflate catalyzed CDC between *N*-*t*Bu nitrones and terminal alkynes using **3** and O_2 as oxidants. Reactions can be performed on a wide array of alkynes and nitrones. Importantly, alkynylated nitrones were successfully transformed to regioisomerically pure 3,5-disubstituted isoxazoles. To our knowledge, this sequence represents a novel approach for the preparation of isoxazoles.

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Supporting Information Available. Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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