Heterocycles

International Edition: DOI: 10.1002/anie.201609401
German Edition: DOI: 10.1002/ange.201609401

Copper/P(tBu)$_3$-Mediated Regiospecific Synthesis of Fused Furans and Naphthofurans

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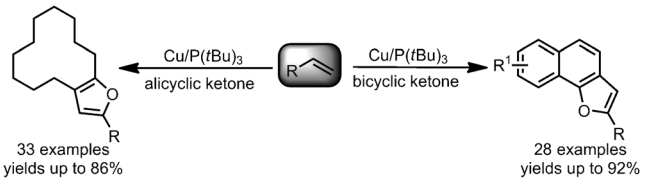
Abstract: *A novel [3+2] cycloaddition between a variety of cyclic ketones and diverse olefins or alkynes can be effectively promoted by copper in combination with the tri-tert-butylphosphine [P(tBu)$_3$] ligand. This protocol exhibits excellent selectivity and provides an exemplary set of fused heterocycles in good to excellent yields. Present strategy also represents an extremely simple and atom-economic way to construct substituted fused furans and naphthofurans from readily available starting materials under mild reaction conditions. The utility of the method is further demonstrated by the synthesis of chiral furans from (R)-(−)-carvone and (S)-(+)-carvone. A plausible mechanism involving the oxidative radical cyclization has been suggested based on experimental observations.*

Fused furans are an important class of heteroaromatic molecules which are invaluable components in a variety of biologically active natural products and important pharmaceuticals.[1] They are also extensively utilized as synthetic intermediates for acyclic, carbocyclic, and heterocyclic compounds in organic synthesis.[2] Consequently, the development of efficient methods for the synthesis of fused furans has attracted considerable interest from synthetic chemists. Research interest in this area has also been encouraged by the occurrence of a number of furano-sesquiterpene natural products having interesting structural skeletons. For example, pallescensin A, furodysinin, marginatafuran, and echinofuran.[3] To date, a variety of inter- and intramolecular strategies have been developed for constructing furan scaffolds. The two traditional methods include Feist–Benary cyclocondensation of 1, 3-dicarbonyl compounds with haloketones[4] and Paal–Knor cyclocondensation of 1,4-dicarbonyl compounds.[5] Other approaches involve the transition-metal-catalyzed cycloisomerizations of alkynyl[6] and allenyl[7] ketones, the palladium-catalyzed decarboxylative cyclization of propargyl β-ketoesters,[8] cycloisomerization of propargylic oxiranes,[9] and the cycloaddition of α-diazocarbonyl compounds with alkynes.[10] However, most of these approaches require either prefunctionalized substrates or multistep procedures. To the best of our knowledge there is no method reported in the literature for the synthesis of fused furans by reacting the cyclic ketones with olefins.

In general direct regiospecific synthesis of substituted fused heterocycles from readily available and cheap chemicals as reactants is a great challenge. Inspired by our recent success in the synthesis of various heterocycles from olefins as starting materials,[11] we herein report a new method joining simple and readily available cyclic ketones and olefins or alkynes to construct fused heterocycles in one step under mild reaction conditions (Scheme 1).



Scheme 1. Synthesis of fused furans and naphthofurans.

Our initial efforts were focused on the reaction of styrene with cyclohexanone. A combination of copper salts and silver salts, gave the furan **A** exclusively, albeit in low yield (Table 1). Among various solvents and oxidants, a DCE and Ag_2CO_3 combination were found to be most effective. We also tested different additives in this system and observed that 1-adamantane carbonyl chloride was most efficient. Among various ligands, P(tBu)$_3$.HBF$_4$ (Fu salt)[12] was found to be most effective for producing **A**. Optimization studies and control experiments confirmed that the transformation does not occur in the absence of either copper or silver salts (entries 1 and 2). However, 1-tetralone produced naphthofuran in 22% yield under these optimized reaction conditions (entry 14). After re-optimization, use of 2 equivalents of $Cu(OAc)_2$ and trifluoroethanol (TFE), as the solvent, was found to be the best for producing naphthofuran in excellent yield (entry 15). External additives were found to be ineffective in increasing the yield of naphthofuran.

At the outset of our study, various cyclic ketones were employed (Table 2). In particular, ketones having electron-donating groups such as *tert*-butyl and *tert*-pentyl gave corresponding fused furans in good to excellent yields (**2b–f**). It was noteworthy that ether-linkage-containing cyclohexanones were suitable substrates and produced the corresponding furans (**2g–j**). Interestingly when we tested this reaction with a natural-product-derived complex molecule, 5α-cholestan-3-one, the desired furan was produced in good yield (**2k**). Moreover, the naturally occurring chiral substrates (*R*)-(−)-carvone and (*S*)-(+)-carvone also reacted smoothly with electronically different styrenes and provided the corresponding furans in synthetically useful yields (**2m–r**). Note that phenyl-substituted cyclohexanones produced a mixture of furan and benzofuran (**2a** and **2l**).

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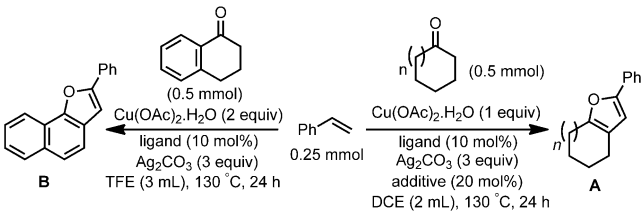
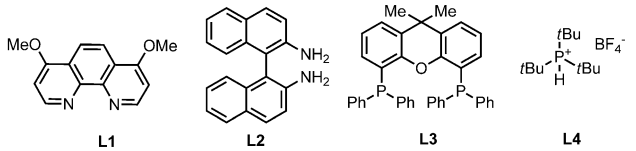
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201609401.

Table 1: Optimization studies and control experiments.[a]

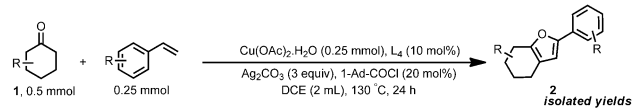


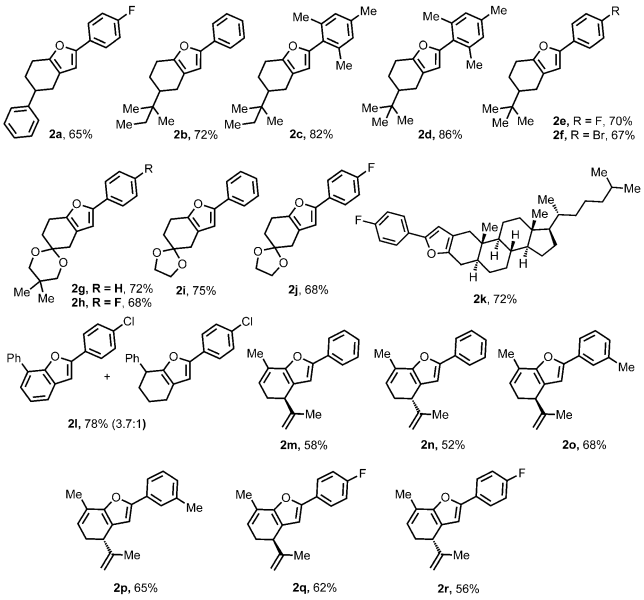


Entry	[Cu salt]	Ligand/[O]	Additive	GC yield [%]
1	$Cu(OAc)_2{\cdot}H_2O$	–	–	0 (**A**/**B**)
2	–	Ag_2CO_3	–	0 (**A**/**B**)
3	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3	–	10 (**A**)
4	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3	PivOH	21 (**A**)
5	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3	TFA	10 (**A**)
6	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3	AcOH	26 (**A**)
7	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3	1-Ad-COCl	30 (**A**)
8	$Cu(OAc)_2{\cdot}H_2O$	**L1**/Ag_2CO_3	1-Ad-COCl	13 (**A**)
9	$Cu(OAc)_2{\cdot}H_2O$	**L2**/Ag_2CO_3	1-Ad-COCl	9 (**A**)
10	$Cu(OAc)_2{\cdot}H_2O$	**L3**/ Ag_2CO_3	1-Ad-COCl	23 (**A**)
11	$Cu(OAc)_2{\cdot}H_2O$	**L4**/Ag_2CO_3	1-Ad-COOH	58 (**A**)
12	$Cu(OAc)_2{\cdot}H_2O$	**L4**/Ag_2CO_3	HCl	23 (**A**)
13	$Cu(OAc)_2{\cdot}H_2O$	**L4**/ Ag_2CO_3	1-Ad-COCl	78 (**A**)[b]
14	$Cu(OAc)_2{\cdot}H_2O$	**L4**/Ag_2CO_3	1-Ad-COCl	22 (**B**)[b]
15	$Cu(OAc)_2{\cdot}H_2O$	**L4**/Ag_2CO_3	–	98 (**B**)[c]

[a] All reactions were carried out under air atmosphere. [b] 1 equiv of $Cu(OAc)_2{\cdot}H_2O$, DCE. [c] 2 equiv of $Cu(OAc)_2{\cdot}H_2O$, TFE solvent. Ad = adamantyl, DCE = 1,2-dichloroethane, Piv = pivaloyl, TFA = trifluoroacetic acid.

Table 2: Scope with respect to substituted cyclohexanones.

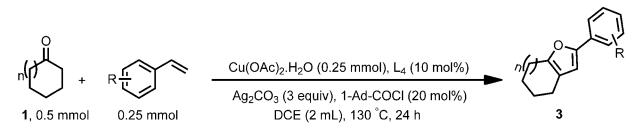


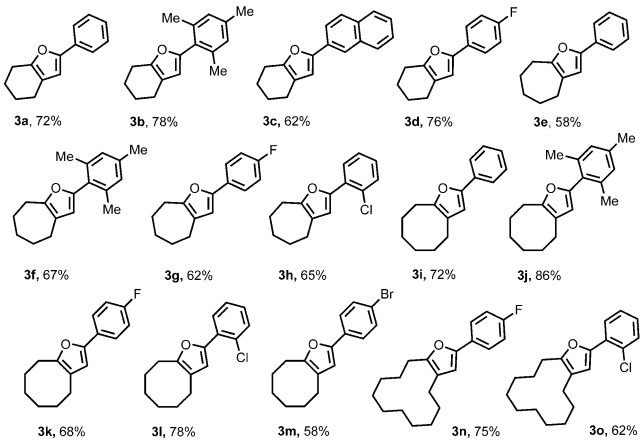


Yields are those of the isolated products.

We then tested the oxidative cyclization of cyclic ketones with different olefins (Table 3). We were pleased to find that various styrenes and 2-vinyl naphthalene served as suitable partners to afford the fused furans. Reactions of the cyclic ketones containing seven-, eight-, and twelve-membered rings successfully afforded the corresponding furans in good yields (**3e–o**).

Table 3: Fused furan synthesis from cyclic ketones and olefins.

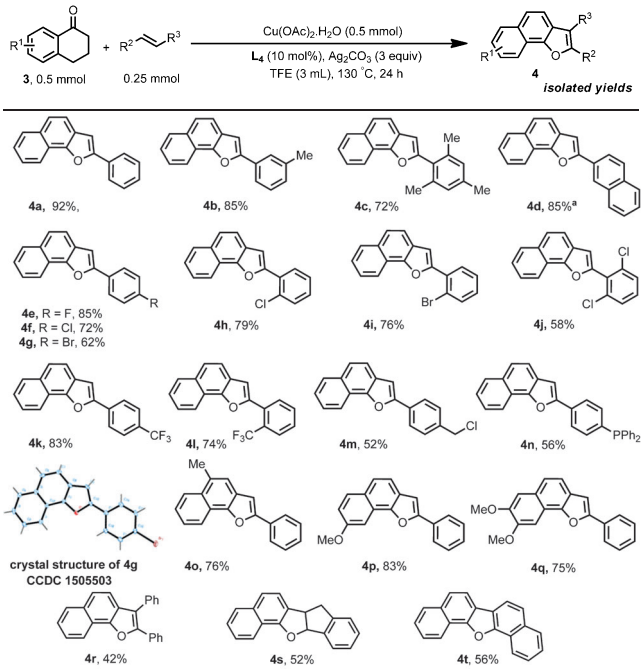




Yields are those of the isolated products.

Having established an efficient synthetic protocol for the synthesis of bicyclic fused furans, we turned our attention to the synthesis of naphthofurans from 1-tetralones. Naphthofurans are an important class of heterocycles which can be found in number of pharmaceuticals and natural products.[13] As a result, a number of synthetic routes leading to differently substituted naphthofurans have been described in the literature.[14] However, synthesis of diversified naphthofurans from readily available starting materials remained a major challenge in organic synthesis. To the best of our knowledge this report is the first on the synthesis of naphthofurans from bicyclic ketones and readily available olefins. A wide variety of olefins participated in the reaction to afford the naphthofurans in good to excellent yields. The reaction was found to be tolerant of electron-donating groups such as methyl (**4b** and **4c**), PPh_2 (**4n**), and electron-withdrawing trifluoromethyl (**4k** and **4l**) and halides (**4e–g**). A naphthalene substituted olefin also produced corresponding naphthofuran with an excellent yield (**4d**). This transformation also tolerates *ortho* substitution on the olefin (**4h–4j**) and methyl and methoxy groups on tetralone (**4o–q**). The formation of naphthofuran has been confirmed by an X-ray crystal structure (**4g**). To further demonstrate the generality and utility of this method we explored the scope with internal olefins (Table 4). A cyclic olefin such as 1,2-dihydro naphthalene gave the naphthofuran **4t**. However in the case of indene, we observed the formation of the dihydronaphthofuran **4s**. Furthermore, we also tested

Table 4: Synthesis of naphthofurans.

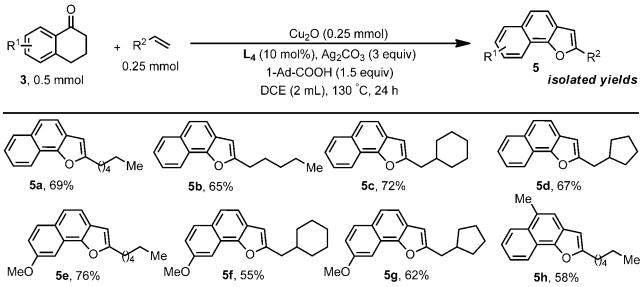


Yields are those of the isolated products. [a] TFE (3 mL):DCE (1 mL).

internal olefins such as *trans*-stilbene, which gave the 2,3-diarylated naphthofuran **4r**.

Next, we replaced aromatic olefins with unactivated and unbiased aliphatic olefins (Table 5). Synthesis of naphthofurans with unactivated olefins is challenging under radical C–H

Table 5: Scope with respect to naphthofurans with unactivated olefins.

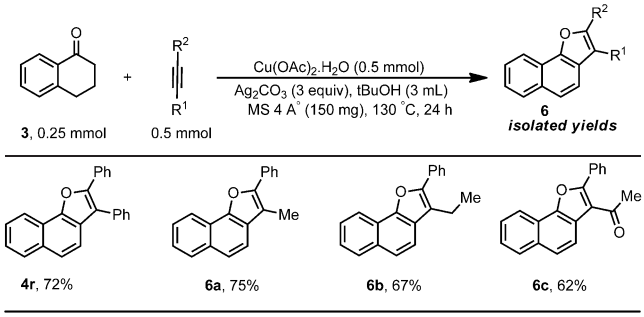


Yields are those of the isolated products. X-ray structure[17] depicted with thermal ellipsoids at 50% probability.

functionalization. Under the current protocol, use of 1-adamantane carboxylic acid was found to be more effective than acid chloride to produce 2-alkylated naphthofuran in good yield. Interestingly, annulation of tetralones with different long-chain (**5a**, **5b**, **5e**, and **5h**), as well as cyclic unactivated olefins (**5c–d** and **5f–g**) produced the corresponding naphthofurans in preparatively useful yields (**5a–h**). Overall, this transformation is effective with both aromatic and aliphatic olefins.

To show the generality of this transformation, we next focused on the synthesis of 2,3-disubstituted naphthofurans from 1-tetralone and internal alkynes (Table 6). Use of *tert*-

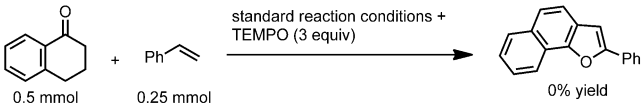
Table 6: Scope of naphthofurans with internal alkynes.



Yields are those of the isolated products.

butanol (*t*BuOH) as the solvent and the addition of a drying agent [4 Å molecular sieves (M.S.)] increased the yield of the desired naphthofuran. Electron-rich alkynes, like 1-phenyl-1-propyne and 1-phenyl-1-butyne, provided the desired naphthofurans **6a** and **6b**, respectively. Similarly, electron-poor 4-phenylbut-3-yn-2-one also underwent annulation with **3** efficiently (**6c**).

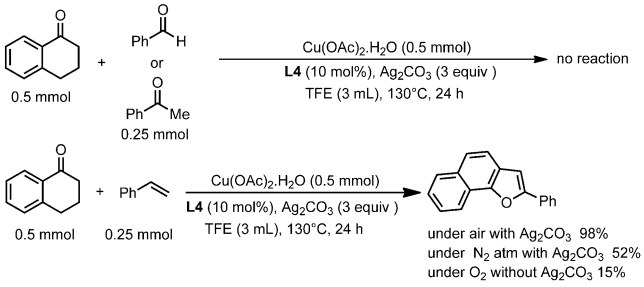
To gain mechanistic insights, we added 3 equivalents of 2,2,6,6-tetramethyl piperidine *N*-oxyl (TEMPO) under the optimized reaction conditions (Scheme 2). Complete inhibition of the formation of the desired product suggested that a radical initiation pathway may be involved in the reaction.



Scheme 2. Radical scavenger experiment.

When the reaction was carried out in the absence of 1-tetralone, a trace amount of benzaldehyde was detected. However, either benzaldehyde or acetophenone (instead of olefin), under the same reaction conditions did not produce the desired product (Scheme 3). These observations likely suggest that the reaction does not involve enol coupling[15] followed by Paal–Knorr cyclocondensation under the present condition.

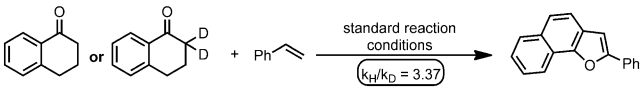
Although 98% naphthofuran was obtained under air, only 52% product was formed under an N_2 atmosphere (Scheme 3). In the absence of silver carbonate, only 15% naphthofuran was produced under O_2. These control experi-



Scheme 3. Control experiments.

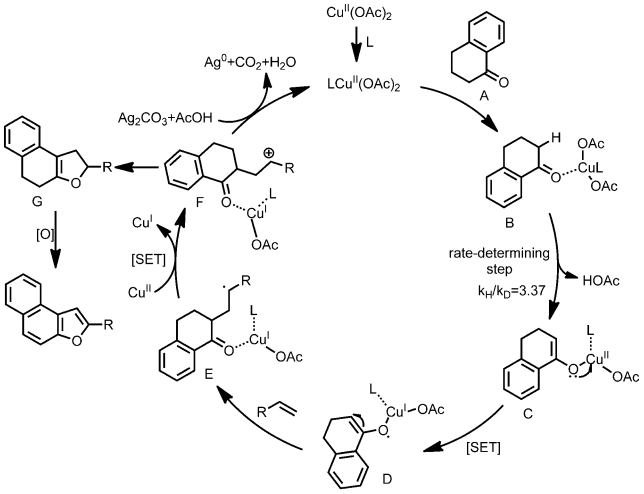
ments suggest that both silver carbonate and aerobic conditions were indispensable for the desired product formation.

To obtain further insights into the mechanism, the order of the reaction was determined with respect to 1-tetralone and styrene. The reaction is first order in tetralone, however a negative order (−1) was established with respect to styrene. The rates with 1-tetralone and [D_2]tetralone were also studied. A kinetic isotope effect (KIE, k_H/k_D) value of 3.37 was obtained, thus indicating that C–H bond cleveage of 1-tetralone is involved in the rate-determining step (Scheme 4). Furthermore, first-order rate dependency of copper acetate has supported our hypothesis.



Scheme 4. Kinetic isotope experiment.

On the basis of the results described above a radical-based mechanism has been outlined in Scheme 5. In situ generated copper-ligand complex coordinates to tetralone to generate the intermediate **B**. Removal of the acetic acid from **B** leads to



Scheme 5. Plausible mechanism.

the intermediate **C**. Single-electron transfer (SET) and tautomerization produce the intermediate **D**. Addition **D** to the β-position of olefin leads to the intermediate **E**. A subsequent SET and intramolecular cyclization results in **G**. Subsequent radical-based dehydrogenation[16] of **G** followed by oxidation gives the desired product. The Cu^I formed in **F** gets oxidized to Cu^{II} by a Cu^I/Ag^I couple.

In summary, we have developed a novel copper-mediated [3+2] cycloaddition of cyclic ketones and either olefins or alkynes. This method represents an extremely simple and efficient method for the synthesis of fused heterocycles from readily available starting materials under mild reaction conditions with exclusive selectivity and good to excellent yields.

Acknowledgements

This activity is supported by CSIR, India (02/(0242)/15/EMR-II). Financial assistance provided by CSIR-New Delhi (fellowship to T.N. and A.D.) is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: copper · cycloaddition · heterocycles · olefins · P ligands

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[17] CCDC 1505503 (**4g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Manuscript received: September 25, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Heterocycles

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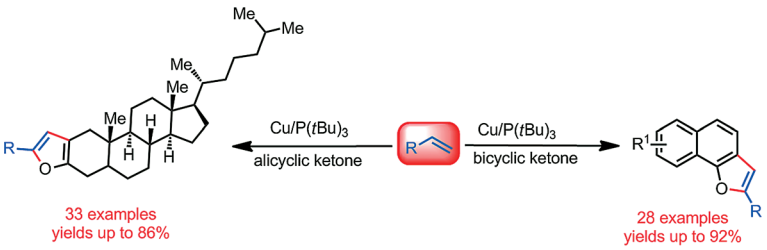
D. Maiti* ——————— ■■■■–■■■■

Copper/P(tBu)$_3$-Mediated Regiospecific Synthesis of Fused Furans and Naphthofurans



Fusion chemistry: A novel [3+2] cycloaddition between a variety of cyclic ketones and olefins is effectively promoted by Cu/P(tBu)$_3$. The protocol provides fused heterocycles in good to excellent yields, and is an atom-economic way to construct fused furans and naphthofurans from readily available starting materials under mild reaction conditions. A mechanism involving an oxidative radical cyclization is suggested.

