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Atom-efficient synthesis of α-alkylidene-*N*-furylimines *via* catalytic vinylcarbene-transfer reactions to carbonyl-ene-nitrile compounds†

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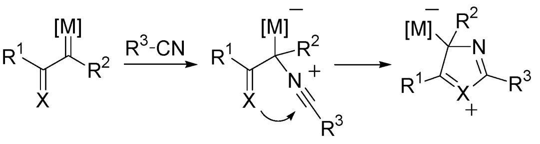
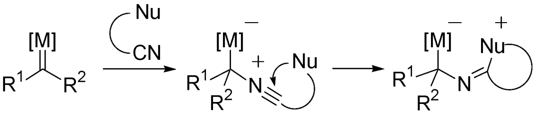
The reaction of carbonyl-ene-nitrile compounds with propargyl carboxylates in the presence of a catalytic amount of $PtCl_2$ afforded the α-alkylidene-*N*-furylimines with high stereo-selectivities.

Catalytic carbene-transfer reactions have been well investigated, aimed at developing facile and efficient access to structurally complex molecules.[1] Among them, addition reactions of rhodium–carbene complexes generated from α-diazocarbonyl compounds to nitriles provides a straightforward method for the synthesis of 1,3-oxazoles.[2] Recently, this method has been expanded to the rhodium-catalyzed synthesis of imidazopyridines[3] and imidazoles.[4] However, to the best of our knowledge, the reported examples have been limited to the reactions between nitriles and carbene species having nucleophilic carbonyl or imino groups α to the carbenoid carbons (eqn (1)).[5] These facts prompted us to investigate the reactions of nitriles which possess nucleophilic moieties in close proximity to the carbon–nitrogen triple bonds (eqn (2)).



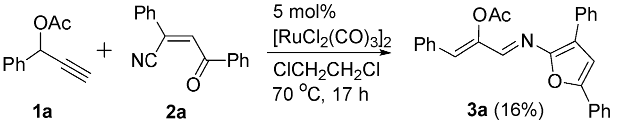
(1)



(2)

Recently, the reaction between propargyl carboxylates and transition metals has received considerable attention as a diazoalkane-free atom-efficient generation method of vinylcarbene complexes.[6] We developed a wide range of catalytic vinylcarbene-transfer reactions using propargyl carboxylates.[7] Thus, we set out our investigation using propargyl carboxylates as carbene precursors and nitriles as carbene acceptors to seek for new reactions as depicted in eqn (2). Herein, we wish to report atom-efficient synthesis of α-alkylidene-*N*-furylimines *via* catalytic vinylcarbene-transfer reactions to carbonyl-ene-nitrile compounds **2** (Scheme 1).[8,9]

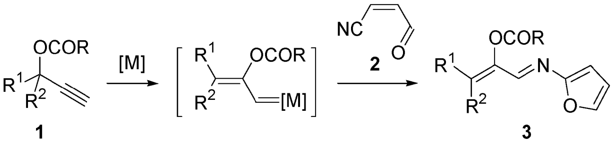
When the reaction of 1-phenyl-2-propynyl acetate **1a** as a carbene precursor with carbonyl-ene-nitrile compound **2a** was carried out in the presence of a catalytic amount of $[RuCl_2(CO)_3]_2$ (5 mol%) in $ClCH_2CH_2Cl$ at 70 °C, α-alkylidene-*N*-furylimine **3a** was obtained in 16% yield as a single stereoisomer (eqn (3)).



(3)

This unusual reaction of a nitrile encouraged us to optimize the reaction conditions. First, reactions of **1a** and **2a** in the presence of several transition metal catalysts were examined. The results are summarized in Table 1. Among the catalysts screened, we found that $PtCl_2$ was superior to $[RuCl_2(CO)_3]_2$, giving **3a** in 27% yield (entry 1). Although other platinum catalysts, such as $PtCl_2(PPh_3)_2$ and $PtCl_4$, exhibited marginal catalytic activity (entries 4 and 5), $[Rh(OAc)_2]_2$, $GaCl_3$, $AuCl_3$, $AuCl(PPh_3)$, $[RuCl_2(p\text{-cymene})]_2$, and $PdCl_2(CH_3CN)_2$ were almost ineffective for the present reaction, **2a** being recovered intact (entries 6–8). This reaction was strongly influenced by the solvent used. Among the solvents examined, toluene was superior to $ClCH_2CH_2Cl$ and THF, and **3a** was obtained in 52% yield (entry 3). In all cases, **2a** was not completely converted to the product even with extended reaction time.[10]

Next, we examined the substrate scope of the reaction using a variety of 1-aryl-2-propynyl carboxylates **1** as carbene precursors in the presence of $PtCl_2$ (Table 2). Reactions of propargyl pivalate **1b** and benzoate **1c** with **2a** (entries 1 and 2) gave α-alkylidene-*N*-furylimines **3b** and **3c**, respectively, with slightly lower yields in comparison with propargyl acetate **1a**. The reaction was sensitive to the electronic features of the aryl group of **1**. Propargyl acetates **1d**, **1e**, and **1f**, which possess electron-withdrawing groups, reacted with **2a** to give the corresponding α-alkylidene-*N*-furylimines **3d**, **3e**, and **3f**, respectively, in good yields (entries 3–5). On the other hand, propargyl acetates **1g** and **1h** having electron-donating groups at the *para*-position of the aryl group produced α-alkylidene-*N*-furylimines in lower yields (entries 6 and 7). These results



Scheme 1 Transition metal-catalyzed reactions of propargyl carboxylates **1** with carbonyl-ene-nitrile compounds **2**.

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† Electronic supplementary information (ESI) available: Experimental details and analytical data are provided. CCDC 755818. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b924752a

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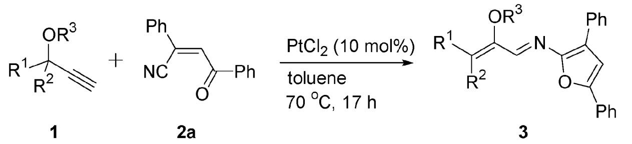
Table 1 Optimization of reaction conditions[a]

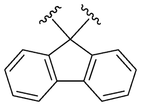
$$\mathbf{1a} + \mathbf{2a} \xrightarrow[\text{solvent, } 70\ ^\circ\text{C, 17 h}]{[\text{M}]\ (10\ \text{mol\%})} \mathbf{3a}$$

Entry	[M]	Solvent	Conv. of **2a**	Yield[b]
1	$PtCl_2$	$ClCH_2CH_2Cl$	32%	27%
2	$PtCl_2$	THF	8%	3%
3	$PtCl_2$	Toluene	66%	52%
4	$PtCl_2(PPh_3)_2$	$ClCH_2CH_2Cl$	3%	1%
5	$PtCl_4$	$ClCH_2CH_2Cl$	28%	21%
6[c]	$[Rh(OAc)_2]_2$	$ClCH_2CH_2Cl$	0%	0%
7	$GaCl_3$	$ClCH_2CH_2Cl$	0%	0%
8	$AuCl_3$	$ClCH_2CH_2Cl$	0%	0%

[a] Reaction conditions: **1a** (0.90 mmol), **2a** (0.30 mmol), [M] (0.030 mmol) in solvent (1.2 mL). [b] Isolated yields. [c] $[Rh(OAc)_2]_2$ (5 mol%).

Table 2 Pt-catalyzed reactions of carbonyl-ene-nitrile compound **2a** with 1-aryl-2-propynyl carboxylates **1**[a]



Entry	R¹	R²	R³		Product	Yield[b]
1	Ph	H	Piv	**1b**	**3b**	47%
2	Ph	H	Bz	**1c**	**3c**	57%
3	$4\text{-}BrC_6H_4$	H	Ac	**1d**	**3d**	64%
4	$4\text{-}CF_3C_6H_4$	H	Ac	**1e**	**3e**	66%
5	C_6F_5	H	Ac	**1f**	**3f**	74%
6	$4\text{-}CH_3C_6H_4$	H	Ac	**1g**	**3g**	38%
7	4-Anisyl	H	Ac	**1h**	**3h**	24%
8			Ac	**1i**	**3i**	80%

[a] Reaction conditions: **1** (0.90 mmol), **2a** (0.30 mmol), $PtCl_2$ (0.030 mmol) in solvent (1.2 mL). [b] Isolated yields.

can be explained by assuming the resonance structures of vinylcarbene complex intermediates (Fig. 1).[7] The substrate scope could be expanded to *tert*-propargyl acetates. The reaction of **1i**[7e] with **2a** gave α-fluoren-9-ylidene-*N*-furylimine **3i** in 80% yield (entry 8). The formation of *Z*- and *anti*-stereoregulated products reflects the intervention of *Z*-vinylcarbene complexes (Fig. 1).

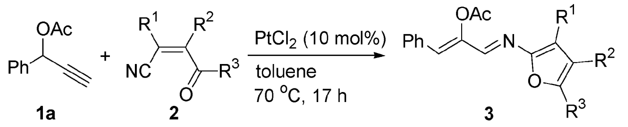
The structure of the product was confirmed by X-ray crystallographic analysis.[11] An ORTEP drawing of **3f** unambiguously shows the *anti* configuration of the imine and *Z*-geometry of the alkenyl moiety (Fig. S1 in ESI†).

N-Furylimines were produced by reactions with various carbonyl-ene-nitrile compounds **2** (Table 3). The reaction of **2b** with propargyl acetate **1a** gave the corresponding α-alkylidene-*N*-furylimine **3j** in 48% yield. Interestingly, a cyano group and an ester group as an R¹ in **2c** and **2d** can be tolerated under these reaction conditions, the corresponding α-alkylidene-*N*-furyl-imines **3k** and **3l** being obtained in good yields. Moreover, cyclohexene-fused carbonyl-ene-nitrile compounds **2e** and **2f** reacted with **1a** to give **3m** and **3n** in 66% and 72% yields, respectively.

The most plausible mechanism for the present reaction is illustrated in Scheme 2. First, platinum-vinylcarbene complex **A** is formed *via* the 1,2-migration of the acetate to an internal carbon atom of the alkyne.[7] Platinum-vinylcarbene complex **A** then reacts with **2** through two possible pathways (path A or B). In path A, nucleophilic attack of a cyano moiety of **2** on the carbenoid carbon would afford metal-containing nitrile ylide intermediate **B**, which then converts to α-alkylidene-*N*-furylimine *via* intramolecular cyclization followed by regeneration of the catalyst. In path B, [2+2] cycloaddition between **A** and **2** followed by ring cleavage generates iminocarbene complex **D**,[12] which undergoes insertion of a carbonyl group to give the α-alkylidene-*N*-furylimine **3** along with regeneration of the catalyst.

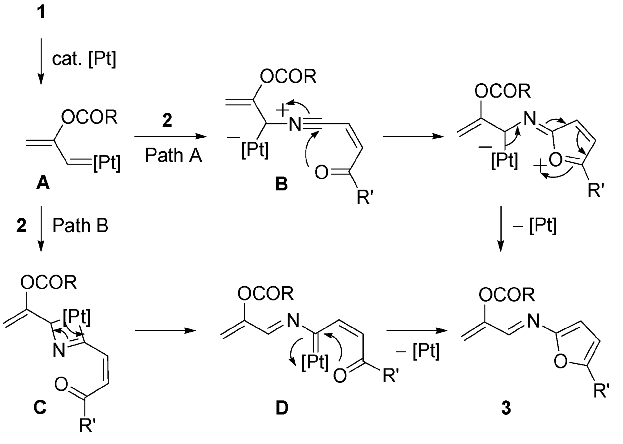
Because α-alkylidene-*N*-furylimines were obtained from the one-pot reaction, we next demonstrated the synthetic application of them to *N*-furyl substituted nitrogen-containing heterocycles.

Table 3 Pt-catalyzed reactions of carbonyl-ene-nitrile compounds **2** with 1-phenyl-2-propynyl acetate **1a**[a]



Entry	R¹	R²	R³		Product	Yield
1	4-Tol	H	Ph	**2b**	**3j**	48%
2	CN	H	Ph	**2c**	**3k**	68%
3	CO_2Et	H	Ph	**2d**	**3l**	58%
4	$–(CH_2)_4–$		Ph	**2e**	**3m**	66%
5	$–(CH_2)_4–$		$4\text{-}CF_3C_6H_4$	**2f**	**3n**	72%

[a] Reaction conditions: **1a** (0.90 mmol), **2** (0.30 mmol), $PtCl_2$ (0.030 mmol) in solvent (1.2 mL). [b] Isolated yields.



Scheme 2 Plausible reaction mechanism.

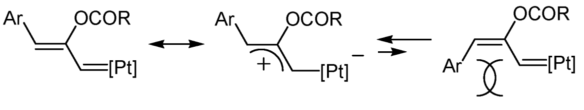


Fig. 1 Proposed structures of Pt-vinylcarbenoids.

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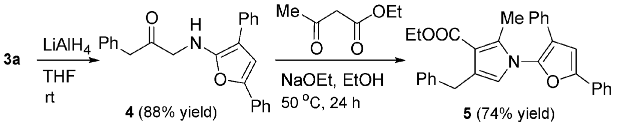

Scheme 3 Synthetic application.

When the reduction of **3a** with $LiAlH_4$ was performed, *N*-(2-furyl)-α-amino ketone **4** was obtained in 88% yield.[13] The subsequent annulation with ethyl acetoacetate afforded *N*-(2-furyl)pyrrole **5** in 74% yield (Scheme 3).[14]

In conclusion, we have demonstrated catalytic carbene transfer reactions to carbonyl-ene-nitrile compounds on the basis of the *in situ* generation of vinylcarbene complexes from propargyl carboxylates leading to α-alkylidene-*N*-furylimine derivatives. The reaction proceeds in a complete atom-economical fashion and provides straightforward access to α-alkylidene-*N*-furylimines, which can be employed as building blocks for the synthesis of nitrogen-containing heterocycles. α-Alkylidene-*N*-furylimines can be considered as coupling products of vinylcarbenes and 2-furylnitrenes.[8,15] Further investigations of the scope and reaction mechanisms, as well as synthetic applications, are currently in progress in our laboratory.

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Notes and references

1 (*a*) F. Z. Dörwald, in *Metal Carbenes in Organic Synthesis*, Wiley-VCH, Weinheim, 1999; (*b*) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861; (*c*) K. H. Dötz, *Metal Carbenes in Organic Synthesis*, Springer-Verlag, Berlin, 2004; (*d*) J. W. Herndon, *Coord. Chem. Rev.*, 2009, **253**, 1517.

2 For recent reviews, see: (*a*) A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, 1991, **91**, 263; (*b*) C. Escolano, M. D. Duque and A Vázquez, *Curr. Org. Chem.*, 2007, **11**, 741.

3 S. Chuprakov, F. W. Hwang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2007, **46**, 4757.

4 T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 14972.

5 Non-catalytic 1,3-dipolar cycloadditions of nitrile ylides, which are formed by reactions of nitriles with carbenes generated from thermal or photochemical decomposition of diazoalkanes, are of special interest. See: (*a*) W. A. Sheppard, G. W. Gokel, W. Webster, K. Betterton and J. W. Timberlake, *J. Org. Chem.*, 1979, **44**, 1717; (*b*) A. S. Kende, P. Hebeisen, P. J. Sanfilippo and B. H. Toder, *J. Am. Chem. Soc.*, 1982, **104**, 4244; (*c*) N. J. Turro, Y. Cha, I. R. Gould, A. Padwa, J. R. Gasdaska and M. Tomas, *J. Org. Chem.*, 1985, **50**, 4415; (*d*) A. Padwa, J. R. Gasdaska, M. Tomas, N. J. Turro, Y. Cha and I. R. Gould, *J. Am. Chem. Soc.*, 1986, **108**, 6739.

6 For recent reviews, see: (*a*) B. Crone and S. F. Kirsch, *Angew. Chem. Int. Ed.*, 2008, **14**, 3514; (*b*) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239; (*c*) K. Ohe and K. Miki, *J. Synth. Org. Chem, Jpn.*, 2009, **67**, 1161.

7 (*a*) K. Miki, K. Ohe and S. Uemura, *Tetrahedron Lett.*, 2003, **44**, 2019; (*b*) K. Miki, K. Ohe and S. Uemura, *J. Org. Chem.*, 2003, **68**, 8505; (*c*) K. Miki, M. Fujita, S. Uemura and K. Ohe, *Org. Lett.*, 2006, **8**, 1741; (*d*) K. Ohe, M. Fujita, H. Matsumoto, Y. Tai and K. Miki, *J. Am. Chem. Soc.*, 2006, **128**, 9270; (*e*) K. Miki, Y. Senda, T. Kowada and K. Ohe, *Synlett*, 2009, 1937.

8 (*Z*)-Carbonyl-ene-nitrile compounds **2** are ring-opened isomers of (2-furyl)nitrenes. Ring-opening of its analogous, (2-pyrazolyl)-nitrenes and (1,2,3-triazolyl)nitrenes to acyclic conjugated nitriles have been investigated. See: (*a*) P. A. S. Smith, W. Resemann and L. O. Krbechek, *J. Am. Chem. Soc.*, 1964, **86**, 2025; (*b*) P. A. S. Smith and H. Founchis, *J. Org. Chem.*, 1973, **38**, 2958; (*c*) D. Suárez and T. L. Sordo, *J. Am. Chem. Soc.*, 1997, **119**, 10291; (*d*) N. Svenstrup, K. B. Simonsen, N. Thorup, J. Brodersen, W. Dehaen and J. Becher, *J. Org. Chem.*, 1999, **64**, 2814.

9 For synthetic applications to *N*-heterocycles, see: (*a*) M. Murai, S. Kawai, K. Miki and K. Ohe, *J. Organomet. Chem.*, 2007, **692**, 579; (*b*) M. Murai, K. Miki and K. Ohe, *J. Org. Chem.*, 2008, **73**, 9174.

10 No reaction of substrate **2a** occurred in the absence of **1a**, and **2a** being recovered intact.

11 See supplementary information for the detail of X-ray crystal analysis data. CCDC 755818 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.

12 For stoichiometric reactions of group 6 Fischer carbene complexes with nitriles leading to iminocarbene complexes, see: (*a*) H. Fischer and S. Zeuner, *J. Organomet. Chem.*, 1987, **327**, 63; (*b*) D. C. Yang, V. Dragisich, W. D. Wulff and J. C. Huffman, *J. Am. Chem. Soc.*, 1988, **110**, 307. The azametallacyclobutene intermediates like **C** were reported by Gevorgyan *et al.* See ref. 3 and 4.

13 Reduction of vinylcarboxylates into corresponding ketones with $LiAlH_4$ has been reported. See: P. Mauleon, J. L. Krinsky and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 4513.

14 *N*-(2-furyl)pyrroles are of biological interest as inhibitor of xanthine oxidase, antagonist on thromboxane A_2, and prostaglandin D_2 receptors. See: (*a*) T. Honma, Y. Hiramatsu and A. Arimura, *PCT Int. Appl*, WO 2000053573, 2000 [*Chem. Abstr*. 2000, **133**, 222579]; (*b*) T. Yagami, T. Honma and G. Katsuura, *PCT Int. Appl*, WO2000030683, 2000 [*Chem. Abstr*. 2000, **133**, 12765]; (*c*) N. Tanimoto and A. Arimura, *PCT Int. Appl*, WO 2001094309, 2001 [*Chem. Abstr*. 2001, **136**, 37614]; (*d*) K. Shimizu, Y. Takigawa, H. Fujikura, M. IIzuka, M. Hiratochi and N. Kikuchi, *PCT Int. Appl*, WO 2008126899, 2008 [*Chem. Abstr*. 2008, **149**, 493522].

15 Recently, cross-coupling of vinylcarbenes generated from propargyl carboxylates with diazoalkane has been reported. See: C. Vovard-Le Bray, S. Dérien and P. H. Dixneuf, *Angew. Chem., Int. Ed.*, 2009, **48**, 1439.