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Synthetic Methods

Gold-Catalyzed Oxidative Cyclization of 1,5-Enynes Using External Oxidants**

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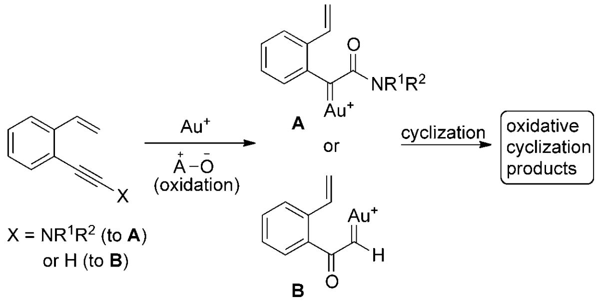
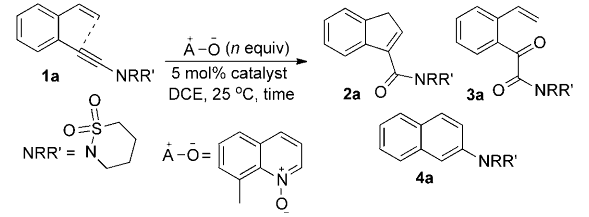
Pd-catalyzed oxidative cyclizations of 1,6-enynes have found useful applications in organic synthesis,[1] but such reactions with Au and Pt catalysis remain largely unexplored.[2] Gold-catalyzed cycloisomerizations of 1,5- and 1,6-enynes provide uncommon and useful carbocyclic frameworks.[3] In the presence of organic oxidants, most enynes fail to produce oxidative cyclization products because oxidations of hypothetical gold–carbenoid intermediates are difficult.[4,5] Herein, we report two new oxidative cyclizations of 1,5-enynes via 5-*endo*-dig and 5-*exo*-dig cyclizations, respectively; both reactions are implemented with Au^I and 8-methylquinoline *N*-oxide. The success of such reactions relies on the prior oxidations of enyne[6] form α-carbonyl carbenoids **A** and **B**, followed by their intramolecular cyclizations (Scheme 1). Terminal alkynes favor the oxidation at the C2 alkynyl carbon atom and aminoalkynes prefer the C1 carbon atom.



Scheme 1. Gold-catalyzed oxidative cyclization of 1,5-enynes. $A^+{-}O^-$ = 8-methylquinoline *N*-oxide.

Table 1 shows the oxidative cyclization of 2-aminoalkynylstyrene **1a**[7] over commonly used Au^I and Pt^{II} catalysts (5 mol%). We employed 8-methylquinoline *N*-oxide, which exhibited greater catalytic activity than diphenylsulfoxide and other pyridine-based oxides.[8–10] Treatment of a solution of 1,5-enyne species **1a** (Table 1, entry 1) and 8-methylquinoline *N*-oxide (1.2 equiv) in 1,2-dichloroethane (DCE, 25 °C) with $[PPh_3AuCl]/[AgNTf_2]$ enabled complete consumption of starting **1a** to give 3-carbonyl-1*H*-indene **2a** and α-carbonyl amide **3a** in 25 % and 45 % yields, respectively. To our delight, the use of $[LAuCl]/[AgNTf_2]$ and $[LAuCl]/[AgSbF_6]$ [L = P(*t*Bu)$_2$(*o*-biphenyl)] gave desired product **2a** exclusively with respective 95 % and 84 % yields (Table 1, entries 2 and 3). A high loading of 8-methylquinoline *N*-oxide (3.0 equiv) gave α-carbonyl amide **3a** in 9 % yield, accompanied by desired **2a** in 75 % yield (Table 1, entry 4). The presence of by-product **3a**, in addition to unreacted **1a**, interfered with other catalysts including $[IPrAuCl]/[AgNTf_2]$ [IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene], $AuCl_3$, and $PtCl_2/CO$ (Table 1, entries 5–7). In the control experiments (Table 1, entries 8 and 9), $AgNTf_2$ or $HNTf_2$ alone failed to show activity for the oxidative cyclization of 1,5-enyne **1a** under similar conditions. In the absence of oxidant, we only obtained aromatization product **4a** from 1,5-enyne **1a** and $[P(tBu)_2(o\text{-biphenyl})AuCl]/[AgNTf_2]$.

Table 1: Oxidative cyclization of 1,5-enynes over various catalysts.



Entry	Catalyst[a]	*n*	*t*	Products[b]
1	$[PPh_3AuCl]/[AgNTf_2]$	1.2	5 min	**2a** (25 %), **3a** (45 %)
2	$[LAuCl]/[AgNTf_2]$	1.2	5 min	**2a** (95 %)
3	$[LAuCl]/[AgSbF_6]$	1.2	5 min	**2a** (84 %)
4	$[LAuCl]/[AgNTf_2]$	3.0	5 min	**2a** (75 %), **3a** (9 %)
5	$[IPrAuCl]/[AgNTf_2]$	1.2	15 min	**2a** (69 %), **3a** (12 %)
6	$AuCl_3$	1.2	12 min	**1a** (24 %), **3a** (58 %)
7	$PtCl_2/CO$	1.2	24 h	**3a** (38 %)
8	$[AgNTf_2]$	1.2	1 h	**2a** (42 %), **3a** (22 %)
9	$HNTf_2$	1.2	1 h	complicated mixture
10	$[LAuCl]/[AgNTf_2]$	0	15 min	**4a** (89 %)

[a] L = P(*t*Bu)$_2$(*o*-biphenyl), [substrate] = 0.25 M. [b] Product yields are reported after separation on a silica column.

We prepared various 1,5-enynes **1b–l** (Table 2) bearing an aminoalkynyl substituent to assess the generality of this oxidative cyclization. Entries 1–5 in Table 2 show the applicability of this catalysis to enynes **1b**–**1f** bearing varied electron-withdrawing amino groups including R^2 = Ms and Ts (Ms = methansulfonyl, Ts = toluene-4-sulfonyl), R^3 = Me, *n*Bu, and phenyl to produce 3-carbonyl-1*H*-indene products **2b**–**2f** in good yields (78–92 %). Similar to its analogue **1a**, propan-4-sultam species **1g** was compatible with this catalysis,

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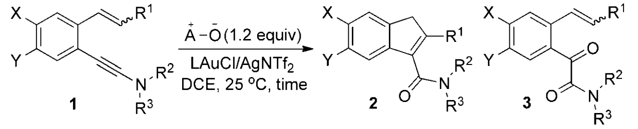
Table 2: Reaction scope for 5-*exo*-dig oxidative cyclizations.



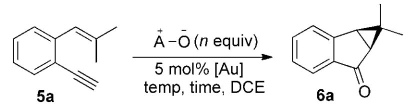
Entry	Enyne[a]	*t* [min]	Products[b]
	X = Y = R^1 = H		
1	R^2 = Ms, R^3 = Me (**1b**)	20	**2b** (78 %)
2	R^2 = Ms, R^3 = Ph (**1c**)	10	**2c** (80 %)
3	R^2 = Ms, R^3 = *n*Bu (**1d**)	5	**2d** (92 %)
4	R^2 = Ts, R^3 = Me (**1e**)	20	**2e** (84 %)
5	R^2 = Ts, R^3 = Ph (**1f**)	5	**2f** (89 %)
6	R^2, R^3 = -$(CH_2)_3SO_2$- (**1g**)	5	**2g** (92 %)
	X = Y = H		
7	R^1 = Me, R^2 = Ms, R^3 = *n*Bu (**1h**)	60	**2h** (49 %), **3h** (32 %)
	R^1 = H, R^2 = Ts, R^3 = Me		
8	X = Cl, Y = H (**1i**)	20	**2i** (83 %)
9	X = H, Y = Cl (**1j**)	20	**2j** (85 %)
10	X = OMe, Y = H (**1k**)	20	**2k** (55 %), **3k** (12 %)
11	X = H, Y = OMe (**1l**)	20	**2l** (75 %)

[a] [Substrate] = 0.25 M. [b] Product yields are reported after separation on a silica column.

giving desired product **2g** in 92 % yield (Table 2, entry 6). We examined this reaction also on 1,2-disubstituted alkene species **1h** (*E*/*Z* = 2.4:1), which gave 3-carbonyl-1*H*-indene **2h** and α-carbonyl amide **3h** (*E*/*Z* = 1:1.4) in 49 % and 32 % yields, respectively (Table 2, entry 7). This catalysis is extensible to 1,5-enynes **1i–l** bearing a chloro and methoxy substituents at the phenyl C4 and C5 carbon atoms, which gave desired **2i–l** in 55–85 % yields (Table 2, entries 8–11). We obtained α-carbonyl amide **3k** in 12 % yield from substrate **1k** bearing a methoxy group *para* to the alkynyl group (Table 2, entry 10).

This gold-catalyzed reaction is applicable to 1,5-enynes (Table 3) bearing a terminal alkyne, as represented by species **5a**. The reactions on this enyne using [P(*t*Bu)$_2$(*o*-biphenyl)AuCl]/[AgNTf$_2$] and [IPrAuCl]/[AgNTf$_2$] catalysts and 8-methylquinoline *N*-oxide (1.2 equiv) in DCE (25 °C) led to complete consumption of starting **5a** within 4–5 h, giving the desired indanone **6a** in comparable yields (38–41 %, Table 3, entries 1 and 2). 8-Methylquinoline *N*-oxide in excess proportion (4 equiv) gave indanone **6a** with increased yields, 52 % and 57 %, respectively for [P(*t*Bu)$_2$(*o*-biphenyl)AuCl]/[AgNTf$_2$] and [IPrAuCl]/[AgNTf$_2$] (Table 3, entries 3 and 4). At 80 °C, the yields of indanone **6a** were increased to 65 % and 58 % for [IPrAuCl]/[AgNTf$_2$] and [P(*t*Bu)$_2$(*o*-biphenyl)AuCl]/[AgNTf$_2$], respectively (Table 3, entries 5 and 6). Notably, treatment of 1,5-enyne **5a** with [IPrAuCl]/[AgNTf$_2$] in the absence of 8-methylquinoline *N*-oxide led to a complicated mixture within 6 min.

Table 3: Oxidative cyclizations of 1,5-enyne **5a** via 5-*endo*-dig mode.

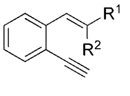
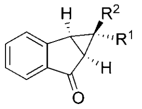
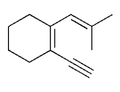
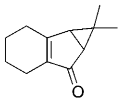
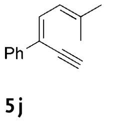
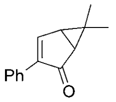
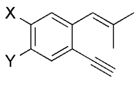
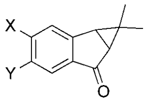


Entry	[Au][a]	*n*	*T* [°C]	*t* [h]	Products[b]
1	[LAuCl]/[AgNTf$_2$]	1.2	25	4	**6a** (38 %)
2	[IPrAuCl]/[AgNTf$_2$]	1.2	25	5	**6a** (41 %)
3	[LAuCl]/[AgNTf$_2$]	4.0	25	4	**6a** (52 %)
4	[IPrAuCl]/[AgNTf$_2$]	4.0	25	34	**6a** (57 %)
5	[LAuCl]/[AgNTf$_2$]	4.0	80	1	**6a** (58 %)
6	[IPrAuCl]/[AgNTf$_2$]	4.0	80	3	**6a** (65 %)
7	[IPrAuCl]/[AgNTf$_2$]	0	25	0.1	complicated mixture

[a] L = P(*t*Bu)$_2$(*o*-biphenyl), [substrate] = 0.25 M. [b] Product yields are reported after separation on a silica column.

The formation of indanone **6a** from 1,5-enyne **5a** represents a 5-*endo-dig* oxidative cyclization. We prepared various 1,5-enynes **5b–p** bearing alterable alkenyl and phenyl substituents to assess the generality of this catalysis, as depicted in Table 4. This reaction is applicable to enyne **5b** bearing a vinyl group, giving the desired indanone **6b** in 53 % yield (Table 4, entry 1). For 1,5-enynes **5c–e** bearing a *trans*-substituted *n*-butyl, phenyl, or cyclopropyl substituent, the resulting products **6c–e** were formed stereoselectively in 69–89 % yields (Table 4, entries 2–4). The stereospecificity of this oxidative cyclization is best manifested by the two diastereomers **5f** and **5g**, which delivered the isomeric indanones **6f** and **6g** in 65 % and 66 % yields, respectively (Table 4,

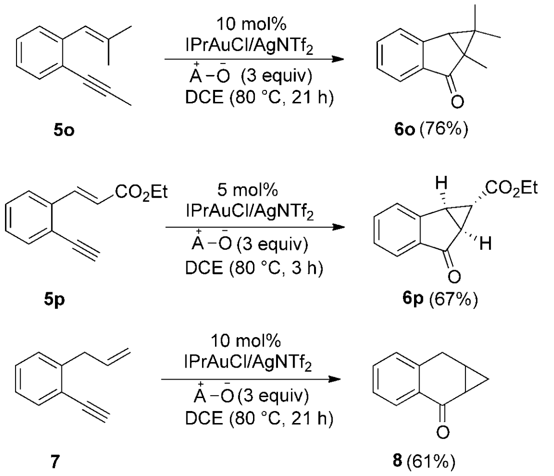
Table 4: Reaction scope for the 5-*endo*-dig oxidative cyclizations.

Entry	Enyne[a]	*t* [h]	Products[b]
			
1	R^1 = R^2 = H (**5b**)	2	**6b** (53 %)
2	R^1 = *n*Bu, R^2 = H (**5c**)	2.5	**6c** (69 %)
3	R^1 = Ph, R^2 = H (**5d**)	3	**6d** (89 %)
4	R^1 = cyclopropyl, R^2 = H (**5e**)	3	**6e** (83 %)
5	R^1 = Ph, R^2 = Me (**5f**)	3.5	**6f** (65 %)
6	R^1 = Me, R^2 = Ph (**5g**)	3.5	**6g** (66 %)
7	R^1, R^2 = -$(CH_2)_5$- (**5h**)	6	**6h** (61 %)
8	 **5i**	2	 **6i** (78 %)
9	 **5j**	2	 **6j** (84 %)
			
10	X = Cl, Y = H (**5k**)	3.5	**6k** (76 %)
11	X = H, Y = Cl (**5l**)	3.5	**6l** (67 %)
12	X = OMe, Y = H (**5m**)	3.5	**6m** (75 %)
13	X = H, Y = OMe (**5n**)	3.5	**6n** (71 %)

[a] [Substrate] = 0.25 M, [IPrAuNTf$_2$] (5 mol %), DCE, 80 °C, 8-methylquinoline *N*-oxide (4 equiv). [b] Product yields are reported after separation on a silica column.

entries 5 and 6). The structures of compounds **6f** and **6g** were confirmed by ^{1}H NOE spectra. The gold-catalyzed reaction of trisubstituted alkene **5h** (Table 4, entry 7) gave expected indanone **6h** in 61% yield. The scope of this oxidative cyclization was further expanded by its applicability to non-benzenoid substrates **5i** and **5j**, which gave cyclopentenone derivatives **6i** and **6j** in 78% and 84% yields, respectively (Table 4, entries 8 and 9). We prepared also new substrates **5k–n** to examine the effects of their phenyl substituents. Good yields (67–76%) were obtained for the resulting products **6k–n** bearing chloro and methoxy substituents at the phenyl C4 and C5 carbon atoms (Table 4, entries 10–13), further illustrating the wide scope of substrates.

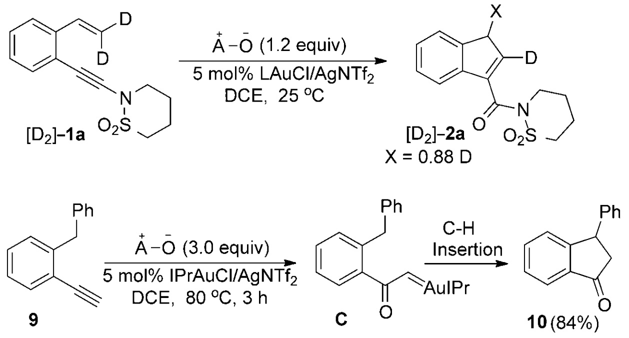
As shown in Scheme 2, this gold-catalyzed reaction is extensible to 1,5-enyne **5o** bearing an internal alkyne, giving desired compound **6o** in 76% yield. For 1,5-enyne **5p** bearing an ester group, we observed no cycloisomerization reaction in hot DCE in the presence of [IPrAuNTf$_2$] only; herein, starting **5p** and [IPrAuNTf$_2$] (5 mol%) were recovered in 84% and 67% yields. Interestingly, enyne **5p** was efficiently transformed into cyclopropyl indanone **6p** as external 8-methylquinoline *N*-oxide (3 equiv) was added to the same system. To our delight, this oxidative cyclization is even applicable to 1,6-enyne **7**, giving desired product **8** in 61% yield under the same conditions.



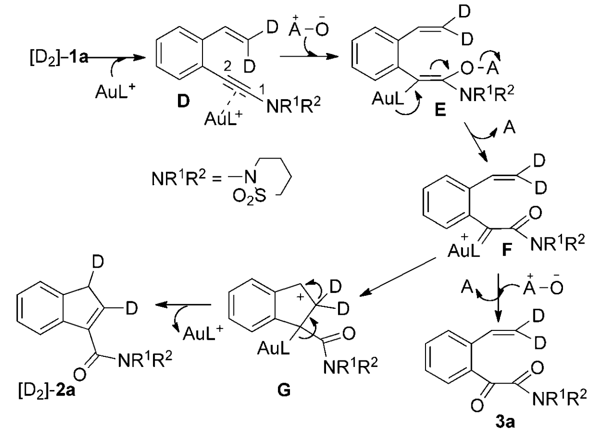
Scheme 2. Applicability of gold-catalyzed oxidative cyclization to additional 1,5- and 1,6-enynes. A$^+$–O$^-$ = 8-methylquinoline *N*-oxide.

We prepared deuterated sample [D$_2$]-**1a** to understand the reaction mechanism of the 5-*exo*-dig oxidative cyclization (Scheme 3). The resulting product [D$_2$]-**2a** contains 0.88 and 1.0 deuterium content at the indenyl C1 and C2 carbon atoms, respectively. We prepared also 2-benzyl-1-ethynylbenzene (**9**), which produced 3-phenylindanone (**10**) in 84% yield in the presence of [IPrAuCl]/[AgNTf$_2$] (5 mol%) and 8-methylquinoline *N*-oxide (3 equiv) in hot dichloroethane (80 °C, 3 h). This transformation clearly asserts the intermediacy of α-carbonyl gold–carbenoid **C**, which undergoes a subsequent C–H insertion to give the observed product **10**.

Accordingly, we propose a plausible mechanism involving α-carbonyl gold–carbenoid intermediate **F** (Scheme 4). The intermediacy of this carbenoid is inferred from the presence of α-carbonyl amide **3a** generated from its secondary oxidation with 8-methylquinoline *N*-oxide.[11] We envisage that the amide functionality of π-alkyne **D** accelerates the nucleophilic attack of 8-methylquinoline *N*-oxide at the alkynyl C1 carbon atom to give alkenylgold intermediate **E**, which undergoes rearrangement to gold carbenoid **F**. To rationalize the deuterium-labeling experiment, species **F** undergoes intramolecular carbocyclization to form benzyl cation **G** that subsequently gives desired [D$_2$]-**2a** by a 1,2-shift of deuterium. We propose also a plausible mechanism to rationalize the formation of indanone **6c** from 1,5-enyne **5c** (Scheme 5). Transformation **9**→**10** in the control experiment (Scheme 3) unambiguously supports the prior oxidation route (path a). We believe that occurrence of the initial 6-*endo*-dig pathway (path b) is difficult because the gold–π-alkyne moiety of species **5c** has the positive charge located primarily at the alkynyl C2 carbon atom. We envisage also that hypothetical benzyl cation **I** would be prone to aromatization to give naphthalene product **J** instead. The prior 6-*endo*-dig route is further excluded because 1,5-enyne **5p** showed no activity in the gold-catalyzed cycloisomerization reaction, but it was active in this oxidative cyclization (see Scheme 2).

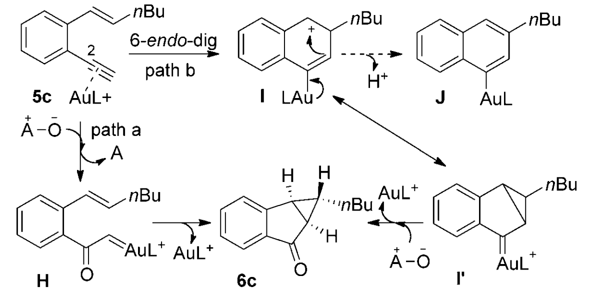


Scheme 3. Control experiments to clarify the reaction mechanism.



Scheme 4. Deuterium-labeling experiments and a plausible mechanism.

In summary, we report two gold-catalyzed oxidative cyclizations of 1,5-enynes using 8-methylquinoline *N*-oxide. For 1,5-enynes **1** bearing an aminoalkynyl substituent, the



Scheme 5. Proposed mechanism for formation of indanone **6c**.

corresponding gold-catalyzed reactions gave 3-carbonyl-1*H*-indene compounds **2** efficiently. The same catalytic reactions on 2-ethynylstyrenes **5** and their non-benzenoid analogues produced cyclopropyl indanone compounds **6** stereoselectively. On the basis of experimental data, we propose that both reactions proceed through prior oxidations of alkyne to form α-carbonyl intermediates, followed by intramolecular carbocyclizations.

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Keywords: cyclization · enynes · gold · homogeneous catalysis · oxidation

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[1] Selected examples: a) L. L. Welbes, T. W. Lyons, K. A. Cychosz, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 5836; b) X. Tong, M. Beller, M. K. Tse, *J. Am. Chem. Soc.* **2007**, *129*, 4905; c) G. Yin, G. Liu, *Angew. Chem.* **2008**, *120*, 5522; *Angew. Chem. Int. Ed.* **2008**, *47*, 5442; d) T. Tsujihara, K. Takenaka, K. Onitsuka, M. Hatanaka, H. Sasai, *J. Am. Chem. Soc.* **2009**, *131*, 3452.

[2] Selected reviews: a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; b) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896; c) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; d) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395; e) S. M. Abu Sohel, R.-S. Liu, *Chem. Soc. Rev.* **2009**, *38*, 2269.

[3] a) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3351; b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271; c) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395.

[4] Only two reports were known for the oxidative cyclizations of 1,6-enynes via oxidative removal of gold-carbenoid intermediates. The work of Toste and co-workers[5a] includes only four 1,6-enyne substrates whereas the second study[5b] involves formation of naphthyl gold–carbenoid that is kinetically stable.

[5] a) C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 5838; b) B. P. Taduri, S. M. Abu Sohel, H.-M. Cheng, R.-S. Liu, *Chem. Commun.* **2007**, 2530.

[6] a) C.-W. Li, K. Pati, G.-Y. Lin, S. M. Abu Sohel, H.-H. Hung, R. S. Liu, *Angew. Chem.* **2010**, *122*, 10087; *Angew. Chem. Int. Ed.* **2010**, *49*, 9891; b) L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258; c) L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550; d) P. W. Davies, A. Cremonesi, N. Martin, *Chem. Commun.* **2011**, *47*, 379; e) B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 14070.

[7] For chemistry of ynamides, see: K. A. Richard DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064.

[8] We obtained the following results using 1.2 equimolar of diphenylsulfoxide and other pyridine-based oxides for the **1a**→**2a** transformation (DCE, 25 °C, 2 h): Ph_2SO (no reaction), 2-bromopyridine *N*-oxide (**2a**, 83 %), 3-bromo-5-methoxycarbonylpyridine *N*-oxide (**2a**, 86 %), and 8-isopropylquinoline *N*-oxide (**2a**, 89 %).

[9] For Ph_2SO-induced redox reactions, see: a) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160; b) G. Li, L. Zhang, *Angew. Chem.* **2007**, *119*, 5248; *Angew. Chem. Int. Ed.* **2007**, *46*, 5156; c) P. W. Davies, S. J.-C. Albrecht, *Chem. Commun.* **2008**, 238; d) A. B. Cuenca, S. Montserrat, K. M. Hossain, G. Mancha, A. Lledós, M. Medio-Simón, G. Ujaque, G. Asensio, *Org. Lett.* **2009**, *11*, 4906.

[10] For nitrogen-based oxides, see Ref. [6b] and a) L. Cui, G. Zhang, Y. Peng, L. Zhang, *Org. Lett.* **2009**, *11*, 1225; b) L. Cui, Y. Peng, L. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 8394; c) H.-S. Yeom, J.-E. Lee, S. Shin, *Angew. Chem.* **2008**, *120*, 7148; *Angew. Chem. Int. Ed.* **2008**, *47*, 7040; d) H.-S. Yeom, Y. Lee, J. Jeong, E. So, S. Hwang, J.-E. Lee, S. S. Lee, S. Shin, *Angew. Chem.* **2010**, *122*, 1655; *Angew. Chem. Int. Ed.* **2010**, *49*, 1611.

[11] C.-F. Xu, M. Xu, Y.-X. Jia, C.-Y. Li, *Org. Lett.* **2011**, *13*, 1556.