Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 2182

Received 25th December 2020,
Accepted 10th February 2021

DOI: 10.1039/d0ob02575e

rsc.li/obc

Metal-free hydroalkoxylation of ynesulfonamides with esters†

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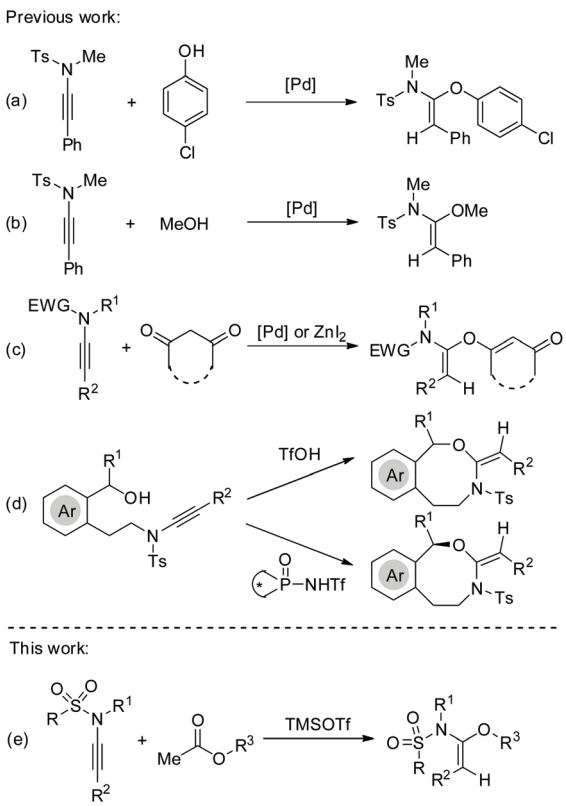
An efficient metal-free hydroalkoxylation reaction of ynesulfonamides with esters under mild conditions is described. Under the catalysis of TMSOTf, various ynesulfonamides are transformed into the corresponding alkoxy-substituted enamides in high yields with complete regioselectivity and high to excellent stereoselectivity.

Recently, the addition of oxygen nucleophiles to the α-carbon of ynamides[1] has captured increasing interest of chemists. And various reactions of ynamides with oxygen nucleophiles have been established.[2,3] For example, acid-mediated or gold-catalyzed hydration of ynamides has been achieved,[4] and palladium-catalyzed or metal-free hydroacyloxylation of ynamides was also disclosed.[4b,5] Despite the diverse additions of oxygen nucleophiles with ynamides that have been developed, the hydroalkoxylation of ynamides which directly provides useful alkoxy-substituted enamides has met with limited success.

Hsung and co-workers first reported the hydroalkoxylation of ynamides with allylic or propargylic alcohols; however, [3,3]-sigmatropic rearrangements which subsequently occurred led to the corresponding amides.[6] Brønsted acid catalyzed hydroalkoxylation of ynamides with simple alcohols such as benzyl alcohol was also unsuccessful.[7] In 2016, Swamy *et al.* described a palladium-catalyzed addition of phenol to ynamides providing the corresponding enamide in 76% yield (Scheme 1a),[8] and later they observed the hydroalkoxylation of ynamides with MeOH as a side reaction during their study on the palladium-catalyzed reduction of ynamides (Scheme 1b).[9] Clavier *et al.* realized the systematic research on the hydroalkoxylation of ynamides to synthesize alkoxy-substituted enamides by the palladium- or ZnI_2-catalyzed addition of 1,3-diones to ynamides (Scheme 1c).[10] Recently, Ye *et al.* reported an intramolecular hydroalkoxylation followed by a [1,3]-rearrangement to synthesize medium lactams, and isolated the intermediate alkoxy-substituted enamides in moderate yields (Scheme 1d).[11] They first achieved the non-metal-catalyzed intramolecular hydroalkoxylation of ynamides with alcohols to produce alkoxy-substituted enamides, and the metal-free intermolecular hydroalkoxylation of ynamides has never been reported. Herein, we present a novel and efficient synthesis of alkoxy-substituted enamides *via* TMSOTf-catalyzed hydroalkoxylation of ynesulfonamides with esters, and various ynesulfonamides



Scheme 1 Hydroalkoxylation reactions of ynamides.

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†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, crystallographic data in CIF and NMR spectra. CCDC 1957512 (**3a**) and 1967694 (**3y′**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob02575e

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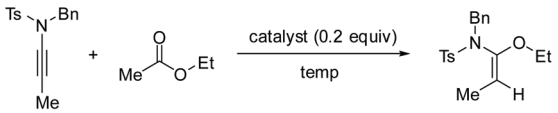
are transformed into their corresponding enamides within short reaction times (Scheme 1e). This outcome not only provides interesting substrates to investigate the synthetic potential of *trans-N,O*-enamides,[5b,10b] but also is exciting as it is in contrast to a previous study, which showed no evidence for useful α-substituted enamide formation from ynamides under TMSOTf.[12]

We began our investigation in the screening of catalysts for the hydroalkoxylation of ynesulfonamide **1a** with ethyl acetate **2a**. Zinc- and aluminum-based Lewis acids were ineffective or less effective (Table 1, entries 1–3), and non-metallic TfOH, Tf_2O and TMSOTf are only marginal (entries 4–6). To our delight, Tf_2NH appeared to be the best promoter, leading to the desired product **3a** in 68% yield within 20 minutes (entry 7), while the Brønsted acid CSA appeared to impede the reaction (entry 8). In order to reduce the by-product caused by the hydrolysis of ynesulfonamide, we lowered the reaction temperature. Follow-up investigation disclosed that there was a noticeable temperature effect on the yield and stereoselectivity (entries 7, 9 and 10), and −40 °C resulted in the highest yield but with the lowest stereoselectivity (entry 10). Further lowering the reaction temperature (−70 °C) led to poor yield and selectivity (entry 11). Owing to the variability of yield and selectivity with the catalyst Tf_2NH, we tried to optimize the reaction with TfOH, Tf_2O and TMSOTf respectively (entries 12–22). A similar phenomenon also occurred under the catalyst TfOH or Tf_2O (entries 12–17). Under the catalysis of TMSOTf, the temperature reduction led to excellent yield and high stereoselectivity, although the stereoselectivity decreased slightly (entry 22 *vs.* entry 19).

Having identified the optimum reaction conditions, the scope of the hydroalkoxylation was investigated as shown in Table 2. Initially, we examined variations in the sulfonamide substitution of ynesulfonamides; the reaction proceeded well giving the desired ethoxy-substituted enamides (**3a–c**) in high yields with high stereoselectivity. A lower, but still quite good yield of **3d** was obtained from the hydroalkoxylation of *N*-Ns-

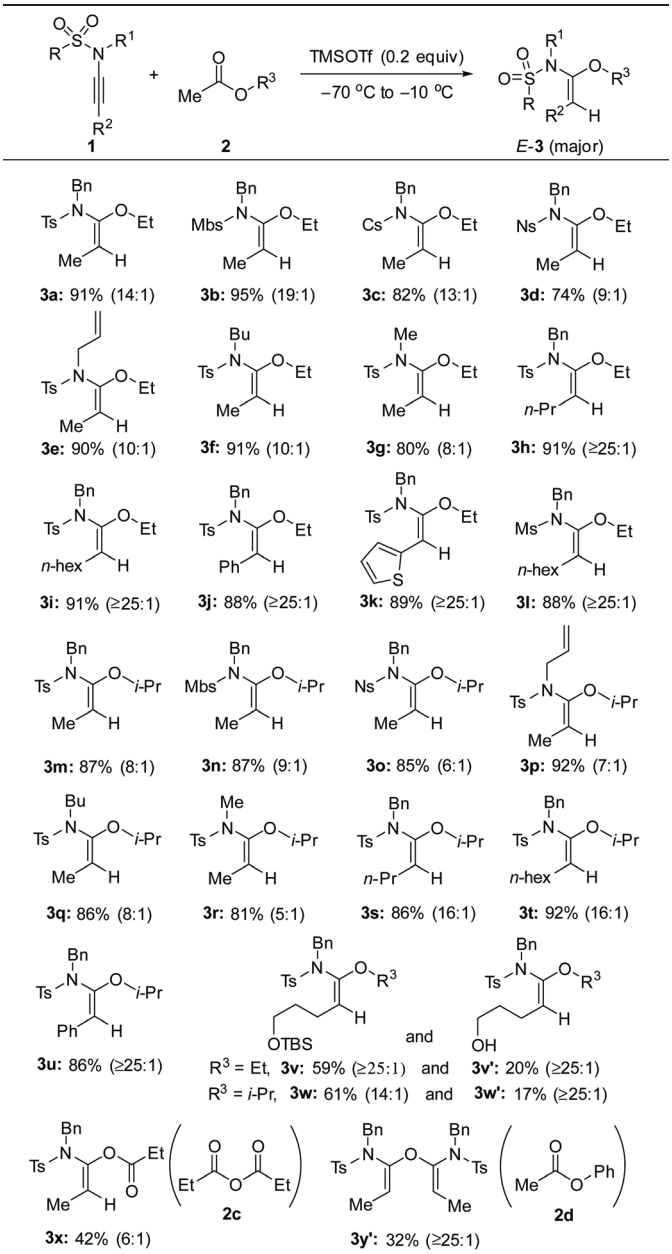
Table 1 Condition optimization of the hydroalkoxylation



Entry[a]	Catalyst	Temp. (°C)	Time (min)	Yield[b] (%)	*E*/*Z*[c]
1	ZnI_2	rt	240	0	—
2	$Zn(OTf)_2$	rt	180	35	≥25 : 1
3	$AlCl_3$	rt	240	18	≥25 : 1
4	TfOH	rt	20	40	≥25 : 1
5	Tf_2O	rt	20	45	≥25 : 1
6	TMSOTf	rt	20	50	≥25 : 1
7	Tf_2NH	rt	20	68	18 : 1
8	CSA	rt	280	Trace	≥25 : 1
9	Tf_2NH	0	20	71	≥25 : 1
10	Tf_2NH	−40	20	90	6 : 1
11	Tf_2NH	−70	60	17[d]	5 : 1
12	TfOH	0	20	72	≥25 : 1
13	TfOH	−40	20	91	8 : 1
14	TfOH	−70	20	82	8 : 1
15	Tf_2O	0	20	72	≥25 : 1
16	Tf_2O	−40	20	89	8 : 1
17	Tf_2O	−70	20	72	8 : 1
18	TMSOTf	0	20	55	≥25 : 1
19	TMSOTf	−20	20	65	≥25 : 1
20	TMSOTf	−40	20	80	14 : 1
21	TMSOTf	−60	20	86	14 : 1
22	TMSOTf	−70	20	91	14 : 1

[a] Unless otherwise noted, reactions were carried out using **1a** (0.20 mmol) with a catalyst (0.04 mmol) in EtOAc (1.0 mL) under N_2. [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy of the unpurified reaction mixture. [d] 77% of **1a** was recovered.

Table 2 Synthesis of alkoxy-substituted enamides[a]



[a] Unless otherwise specified, reactions were carried out using **1** (0.20 mmol), **2** (1.0 mL) and TMSOTf (0.04 mmol) under N_2. *E*/*Z* ratio in parenthesis. Mbs = *para*-methoxy-benzene-sulfonyl; Cs = *para*-chloro-benzene-sulfonyl; Ns = *para*-nitro-benzene-sulfonyl.

substituted ynamide **1d**, presumably due to its low reactivity. These examples revealed that the stronger the electron-donating ability of the substitution on the aromatic group, the better the yield and stereoselectivity. Other *N*-allyl- and alkyl-substituted ynesulfonamides or alkyl- and aryl-terminated ynesulfonamides were also compatible with the conditions affording the desired products (**3e–k**) in high yields with high to excellent stereoselectivity, even for the heteroaromatic substituted ynesulfonamide **1k**. Meanwhile, a significant effect has been detected with respect to the terminal substitutions: the greater the steric hindrance, the better the reaction stereoselectivity. And we were also delighted to find that the high-reactivity *N*-Ms-substituted ynamide **1l** underwent highly effective hydroalkoxylation to furnish ethoxy-substituted enamide **3l** in high yield with excellent stereoselectivity. Subsequently, isopropyl acetate instead of ethyl acetate was subjected to this protocol. Various substituted ynesulfonamides reacted with isopropyl acetate smoothly and produced the isopropoxy-substituted enamides (**3m–u**) in high yields with high to excellent stereoselectivity. It is worth mentioning that ynesulfonamide **1m** bearing the terminal TBS ether moiety could also generate the corresponding alkoxy-substituted enamides **3v** and **3w** at high conversions, accompanied by small amounts of enamides **3v′** and **3w′** bearing the hydroxyl group. Propionic anhydride **2c**, the reactivity of which is high, could also afford the desired enamide **3x**, albeit with a low yield. However, for the low-reactivity phenyl acetate **2d**, no desired product was isolated, but 32% yield of the by-product enamide **3y′** was formed. For the reaction of terminally unsubstituted ynamide **1n** with ethyl acetate **2a**, no desired enamide was obtained, and most of the ynamide **1n** was hydrolyzed to an amide in 86% yield. Also, no desired product was obtained for TIPS-substituted ynamide **1o**; 36% yield of amine was generated with 55% of the starting material **1o** recovered.[13] All the isolated alkoxy-substituted enamides **3** in the pure state showed good stability even in chloroform.[10] Last and most importantly, the X-ray crystallographic analysis of the major isomer reveals that it is *E*-**3a** (Fig. 1);[14] the configurations of other enamides **3** were assigned by NOESY experiments.

Then, we tried to expand the reaction scope beyond *N*-sulfonyl ynamides. For example (Scheme 2), no desired enamide was isolated from the reaction of oxazolidinone-substituted ynamide **4** with ethyl acetate **2a**, instead ester **6**[15] was formed in 83% yield, which is presumably due to the further hydrolysis of highly reactive enamide **5**.

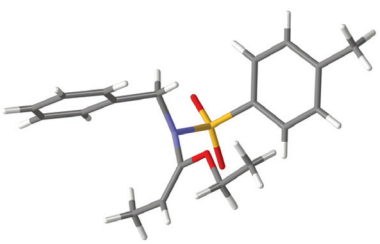
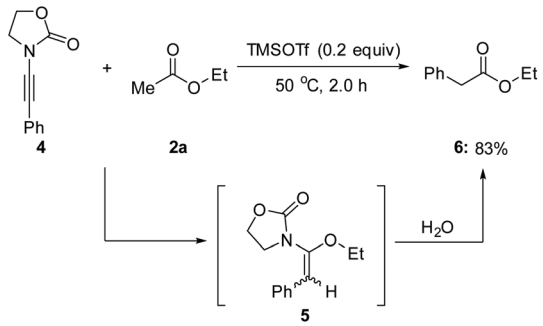


Fig. 1 X-ray structure of *E*-**3a**.



Scheme 2 Hydroalkoxylation reactions of oxazolidinone-substituted ynamide **4**.

Conclusions

In conclusion, we have showcased here a novel and efficient TMSOTf-catalyzed hydroalkoxylation reaction of ynesulfonamides with esters. This methodology provides a general and straightforward pathway to construct a diverse array of alkoxy-substituted enamides in high yields with complete regioselectivity and high to excellent stereoselectivity. And such enamide syntheses are applicable to diversified sulfonamide-derived ynamides. More importantly, this strategy first realized the metal-free intermolecular hydroalkoxylation of ynamides with esters for the synthesis of alkoxy-substituted enamides. Further studies on the mechanism and the application of this hydroalkoxylation are currently underway in our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 81803406 and U1804283) and the Foundation of Henan Educational Committee (19A150009) for financial support.

Notes and references

1 For recent reviews on the chemistry of ynamides, see: (*a*) J. Luo, G.-S. Chen, S.-J. Chen, J.-S. Yu, Z.-D. Li and Y.-L. Liu, *ACS Catal.*, 2020, **10**, 13978; (*b*) C. C. Lynch, A. Sripada and C. Wolf, *Chem. Soc. Rev.*, 2020, **49**, 8543; (*c*) C. Mahe and K. Cariou, *Adv. Synth. Catal.*, 2020, **362**, 4820; (*d*) F.-L. Hong and L.-W. Ye, *Acc. Chem. Res.*, 2020, **53**, 2003; (*e*) X. Zhou, Z. Liang and X.-N. Wang, *Chin. J. Org. Chem.*, 2020, **40**, DOI: 10.6023/cjoc202009025; (*f*) B. Zhou, T.-D. Tan, X.-Q. Zhu, M. Shang and L.-W. Ye, *ACS Catal.*, 2019, **9**, 6393; (*g*) R. H. Dodd and K. Cariou, *Chem. – Eur. J.*, 2018, **24**, 2297; (*h*) B. Prabagar, N. Ghosh and A. K. Sahoo, *Synlett*, 2017, 2539; (*i*) G. Duret, V. Le Fouler, P. Bisseret,

V. Bizet and N. Blanchard, *Eur. J. Org. Chem.*, 2017, 6816; (*j*) F. Pan, C. Shu and L.-W. Ye, *Org. Biomol. Chem.*, 2016, **14**, 9456; (*k*) A. M. Cook and C. Wolf, *Tetrahedron Lett.*, 2015, **56**, 2377; (*l*) G. Evano, C. Theunissen and M. Lecomte, *Aldrichimica Acta*, 2015, **48**, 59; (*m*) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski and R. P. Hsung, *Acc. Chem. Res.*, 2014, **47**, 560; (*n*) N. Weding and M. Hapke, *Chem. Soc. Rev.*, 2011, **40**, 4525; (*o*) G. Domínguez and J. Pérez-Castells, *Chem. Soc. Rev.*, 2011, **40**, 3430; (*p*) C. Madelaine, V. Valerio and N. Maulide, *Chem. – Asian J.*, 2011, **6**, 2224; (*q*) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064; (*r*) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840; (*s*) L. Ackermann and H. K. Potukuchi, *Org. Biomol. Chem.*, 2010, **8**, 4503.

2 selected references on the oxidation of ynamides, see: (*a*) T. Baker and P. W. Davies, *Eur. J. Org. Chem.*, 2019, 5201–5204; (*b*) D. Zhang, J. Man, Y. Chen, L. Yin, J. Zhong and Q.-F. Zhang, *RSC Adv.*, 2019, **9**, 12567; (*c*) F. Sánchez-Cantalejo, J. D. Priest and P. W. Davies, *Chem. – Eur. J.*, 2018, **24**, 17215; (*d*) X.-L. Han, X.-G. Liu, E. Lin, Y. Chen, Z. Chen, H. Wang and Q. Li, *Chem. Commun.*, 2018, **54**, 11562; (*e*) C.-M. Wang, L.-J. Qi, Q. Sun, B. Zhou, Z.-X. Zhang, Z.-F. Shi, S.-C. Lin, X. Lu, L. Gong and L.-W. Ye, *Green Chem.*, 2018, **20**, 3271; (*f*) Z.-X. Zhang, B.-H. Zhu, P.-X. Xie, J.-Q. Tang, X.-L. Li, C. Zhu, Y.-W. Yin and L.-W. Ye, *RSC Adv.*, 2018, **8**, 18308; (*g*) X. Liu, Z.-X. Zhang, B. Zhou, Z.-S. Wang, R.-H. Zheng and L.-W. Ye, *Org. Biomol. Chem.*, 2017, **15**, 10156; (*h*) A. Ragupathi, V. P. Charpe, A. Sagadevan and K. C. Hwang, *Adv. Synth. Catal.*, 2017, **359**, 1138; (*i*) F. Pan, X.-L. Li, X.-M. Chen, C. Shu, P.-P. Ruan, C.-H. Shen, X. Lu and L.-W. Ye, *ACS Catal.*, 2016, **6**, 6055; (*j*) H. Huang, L. Tang, Q. Liu, Y. Xi, G. He and H. Zhu, *Chem. Commun.*, 2016, **52**, 5605; (*k*) L. Li, C. Shu, B. Zhou, Y.-F. Yu, X.-Y. Xiao and L.-W. Ye, *Chem. Sci.*, 2014, **5**, 4057; (*l*) F. Pan, S. Liu, C. Shu, R.-K. Lin, Y.-F. Yu, J.-M. Zhou and L.-W. Ye, *Chem. Commun.*, 2014, **50**, 10726; (*m*) C.-H. Shen, L. Li, W. Zhang, S. Liu, C. Shu, Y.-E. Xie, Y.-F. Yu and L.-W. Ye, *J. Org. Chem.*, 2014, **79**, 9313; (*n*) L.-Q. Yang, K.-B. Wang and C.-Y. Li, *Eur. J. Org. Chem.*, 2013, 2775; (*o*) Y. Minko, M. Pasco, L. Lercher, M. Botoshansky and I. Marek, *Nature*, 2012, **490**, 522; (*p*) R. B. Dateer, K. Pati and R.-S. Liu, *Chem. Commun.*, 2012, **48**, 7200; (*q*) P. W. Davies, A. Cremonesi and N. Martin, *Chem. Commun.*, 2011, **47**, 379; (*r*) C.-F. Xu, M. Xu, Y.-X. Jia and C.-Y. Li, *Org. Lett.*, 2011, **13**, 1556; (*s*) A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad and R.-S. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 15372.

3 (*a*) L. You, Z. F. Al-Rashid, R. Figueroa, S. K. Ghosh, G. Li, T. Lu and R. P. Hsung, *Synlett*, 2007, 1656; (*b*) K. C. M. Kurtz, R. P. Hsung and Y. Zhang, *Org. Lett.*, 2006, **8**, 231; (*c*) H. Liu, Y. Yang, J. Wu, X.-N. Wang and J. Chang, *Chem. Commun.*, 2016, **52**, 6801; (*d*) L. Chen, Y.-M. Cui, Z. Xu, J. Cao, Z.-J. Zheng and L.-W. Xu, *Chem. Commun.*, 2016, **52**, 11131; (*e*) S. Bhunia, C.-J. Chang and R.-S. Liu, *Org. Lett.*, 2012, **14**, 5522; (*f*) J. Oppenheimer, W. L. Johnson, M. R. Tracey, R. P. Hsung, P.-Y. Yao, R. Liu and K. Zhao, *Org. Lett.*, 2007, **9**, 2361.

4 (*a*) H. Huang, L. Tang, Y. Xi, G. He and H. Zhu, *Tetrahedron Lett.*, 2016, **57**, 1873; (*b*) S. Xu, J. Liu, D. Hu and X. Bi, *Green Chem.*, 2015, **17**, 184; (*c*) N. Ghosh, S. Nayak and A. K. Sahoo, *Chem. – Eur. J.*, 2013, **19**, 9428; (*d*) G. Compain, K. Jouvin, A. Martin-Mingot, G. Evano, J. Marrot and S. Thibaudeau, *Chem. Commun.*, 2012, **48**, 5196; (*e*) X. Jin, K. Yamaguchi and N. Mizuno, *Chem. Lett.*, 2012, **41**, 866; (*f*) S. Kramer, J. L. H. Madsen, M. Rottländer and T. Skrydstrup, *Org. Lett.*, 2010, **12**, 2758.

5 (*a*) A. M. Cook and C. Wolf, *Angew. Chem., Int. Ed.*, 2016, **55**, 2929; (*b*) L. Hu, S. Xu, Z. Zhao, Y. Yang, Z. Peng, M. Yang, C. Wang and J. Zhao, *J. Am. Chem. Soc.*, 2016, **138**, 13135; (*c*) D. L. Smith, W. R. F. Goundry and H. W. Lam, *Chem. Commun.*, 2012, **48**, 1505.

6 (*a*) J. A. Mulder, R. P. Hsung, M. O. Frederick, M. R. Tracey and C. A. Zificsak, *Org. Lett.*, 2002, **4**, 1383; (*b*) N. P. Grimster, D. A. A. Wilton, L. K. M. Chan, C. R. A. Godfrey, C. Green, D. R. Owen and M. J. Gaunt, *Tetrahedron*, 2010, **66**, 6429; (*c*) M. O. Frederick, R. P. Hsung, R. H. Lambeth, J. A. Mulder and M. R. Tracey, *Org. Lett.*, 2003, **5**, 2663; (*d*) K. C. M. Kurtz, M. O. Frederick, R. H. Lambeth, J. A. Mulder, M. R. Tracey and R. P. Hsung, *Tetrahedron*, 2006, **62**, 3928.

7 B. Peng, X. Huang, L.-G. Xie and N. Maulide, *Angew. Chem., Int. Ed.*, 2014, **53**, 8718.

8 A. Siva Reddy, A. L. Siva Kumari, S. Saha and K. C. Kumara Swamy, *Adv. Synth. Catal.*, 2016, **358**, 1625.

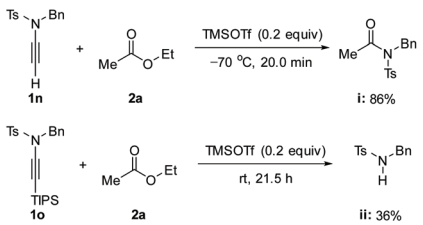
9 A. Siva Reddy and K. C. Kumara Swamy, *Angew. Chem., Int. Ed.*, 2017, **56**, 6984.

10 (*a*) L. V. Graux, H. Clavier and G. Buono, *ChemCatChem*, 2014, **6**, 2544; (*b*) R. Plamont, L. V. Graux and H. Clavier, *Eur. J. Org. Chem.*, 2018, 1372.

11 the metal-free intramolecular hydroalkoxylation followed by a [1,3]-rearrangement, see: B. Zhou, Y.-Q. Zhang, K. Zhang, M.-Y. Yang, Y.-B. Chen, Y. Li, Q. Peng, S.-F. Zhu, Q.-L. Zhou and L.-W. Ye, *Nat. Commun.*, 2019, **10**, 3234.

12 J. A. Mulder, K. C. M. Kurtz, R. P. Hsung, H. Coverdale, M. O. Frederick, L. Shen and C. A. Zificsak, *Org. Lett.*, 2003, **5**, 1547.

13 For the reaction of terminally unsubstituted ynamide **1n** with ethyl acetate **2a**, and TIPS-substituted ynamide **1o** with ethyl acetate **2a**.



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14 For the crystal data of **3a** and **3y′**, see the ESI.†

15 Y. Li, Z. Wang and X.-F. Wu, *Green Chem.*, 2018, **20**, 969.