Organic LETTERS

Letter

pubs.acs.org/OrgLett

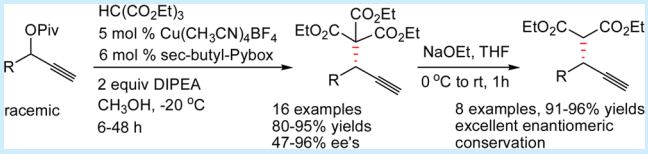
Trialkyl Methanetricarboxylate as Dialkyl Malonate Surrogate in Copper-Catalyzed Enantioselective Propargylic Substitution

Guanxin Huang, Cang Cheng, Luo Ge, Beibei Guo, Long Zhao, and Xiaoyu Wu*

Department of Chemistry, College of Sciences, Shanghai University 99 Shangda Road, Shanghai 200444, China

Supporting Information

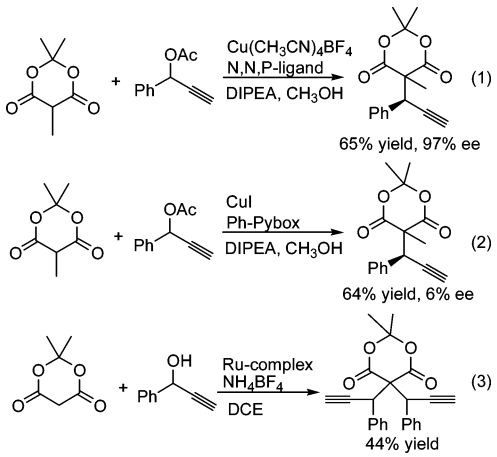
ABSTRACT: The first copper-catalyzed enantioselective propargylation of trialkyl methantricarboxylate with propargylic alcohol derivatives was developed. The tricarboxylate unit in the obtained adducts could be easily transformed into a malonate moiety by treating with *in situ* generated NaOEt in excellent yield without racemization.



Owing to the broad spectrum of reactivity of the alkyne functionality, addition of various nucleophiles to propargylic alcohols or their derivatives has long been pursued by quite a number of research groups.[1] Early studies in this area included the Nicholas reaction via the activation of propargylic alcohol by formation of a cobalt−alkyne complex with a stoichiometric amount of $Co_2(CO)_8$.[2] In 1994, the catalytic version of this process was first implemented by Murahashi and co-workers, wherein aminations of propargyl phosphates and acetates were promoted by a copper complex.[3] Since then, a variety of methodologies have been successfully developed for catalyzed propargylic substitution of propargylic alcohols and their derivatives.[1] Meanwhile, asymmetric versions of this catalytic process have been developed by several research groups employing terminal alkyne propargylic alcohols or their derivatives as reaction partners.[4−8] In particular, since 2000 Nishbayashi and coauthors reported a series of findings on propargylation reactions catalyzed by a thiolate-bridged diruthenium complex.[1c,f] These reactions were rendered asymmetric when chiral disulfides were employed to generate ruthenium complexes.[4] Meanwhile, some other groups, e.g. Marrsaveen's group,[5] Hou's group,[6] and Hu's group,[7] employed combinations of copper salts and chiral ligands as catalysts for reactions between various nucleophiles and propargylic alcohol derivatives.

Despite these achievements, to our knowledge, a successful example of catalyzed enantioselective addition of dialkyl malonate to propargylic alcohol derivatives, bearing either an internal or a terminal alkyne moiety, remains unknown. Since such propargylic substitution can provide access to synthetically useful γ,δ-alkynyl malonates, alternative methods have been highly sought after. The most related successful example was reported by Hu et al., employing methyl substituted Meldrum's acid as a nucleophile catalyzed by a Cu−N,N,P-ligand complex leading to the desired propargylic substituted product in moderate yield and excellent ee (Scheme 1, eq 1).[7c] The same reaction was also conducted by Maarseveen et al., employing a Cu−Pybox complex as the catalyst affording the desired product in moderate yield and low ee (eq 2).[5b] Unsubstituted Meldrum's acid led to the double propargylation product, when

Scheme 1. Previous Examples of Propargylation of Meldrum's Acid



an achiral Ru-complex was recruited as the catalyst (eq 3).[9] Replacing Meldrum's acid with dimethyl malonate in this catalysis system gave only a mixture of unidentified products with complete consumption of the starting propargylic alcohol.

Based on these observations, dialkyl malonate or Meldrum's acid might be unfit for Ru- or Cu-catalyzed addition to progargylic alcohols or their derivatives. In the search for a suitable malonate surrogate for this type of reaction, we envisioned that trialkyl methanetricarboxylate, the pK_a of which approximately equals that of Meldrum's acid (ca. 7.3),[10] might provide a good opportunity. Trialkyl methanetricarboxylates, which can be generally prepared from dialkyl malonates via deprotonation and subsequent addition to alkyl chloroformate, have long been employed as masked malonates.[11] Therefore, we considered the possibility of performing an alternative and unprecedented propargylation reaction with trialkyl methanetricarboxylate, the propargylated products of which could be

Received: August 26, 2015

 © XXXX American Chemical Society

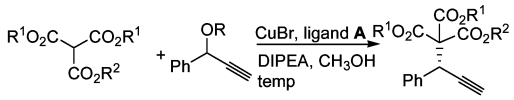
DOI: 10.1021/acs.orglett.5b02463
Org. Lett. XXXX, XXX, XXX−XXX

readily converted to malonate derivatives after appropriate elaboration. Herein, we report the successful implementation of this asymmetric catalytic process leading to the propargylated products in excellent yields and good to excellent ee's.

Recently, copper−Pybox complexes were frequently recruited by several research groups for enantioselective propargylic substitution employing terminal alkyne propargylic alcohol derivatives as reaction components, via formation of copper allenylidene complexes as key intermediates.[12] Two very recent examples are etherification of propargylic esters with alcohols or phenols reported by Nishibayashi et al.,[12b] and propargylation of 3-substituted indoles at indolic C3 position reported by You et al.[8] Given the success of this catalytic system in propargylation, we anticipated that it could be extended to the reaction between a trialkyl methanetricarboxylate and a propargylic alcohol derivative.

To this end, we first examined the reaction between triethylmethanetricarboxylate (TEMT, **1a**) and 1-phenylprop-2-ynyl acetate (**2a**) promoted by a copper complex *in situ* generated from CuBr (10 mol %) and (*S*)-*sec*-butyl-Pybox (Ligand **A**, 12 mol %) at room temperature with methanol as solvent and DIPEA as base (Table 1, entry 1). As expected, the

Table 1. Initial Screening of Reaction Conditions for Propargylic Substitution of Trialkyl Methanetricarboxylate[a]



1a: $R^1 = R^2 = Et$ **2a**: R = Ac **3ac**: $R^1 = R^2 = Et$
1b: $R^1 = R^2 = Me$ **2b**: R = Boc **3bc**: $R^1 = R^2 = Me$
1c: $R^1 = Et$, $R^2 = t$-bu **2c**: R = Piv **3cc**: $R^1 = Et$, $R^2 = t$-bu
1d: $R^1 = Me$, $R^2 = t$-bu **3dc**: $R^1 = Me$, $R^2 = t$-bu
1e: $R^1 = Et$, $R^2 = Bn$ **3ec**: $R^1 = Et$, $R^2 = Bn$

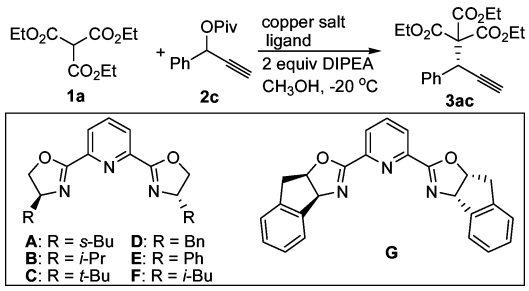
entry	1	2	3	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	**2a**	**3ac**	20	3	80	31
2	**1a**	**2a**	**3ac**	0	10	83	68
3	**1a**	**2a**	**3ac**	−20	24	80	76
4	**1a**	**2b**	**3ac**	−20	24	83	74
5	**1a**	**2c**	**3ac**	−20	20	91	83
6	**1b**	**2c**	**3bc**	−20	20	87	75
7	**1c**	**2c**	**3cc**	−20	20	87	81
8[d]	**1d**	**2c**	**3dc**	−20	20	86	71
9[e]	**1e**	**2c**	**3ec**	−20	20	85	79

[a]General conditions: **1** (0.2 mmol), **2** (0.24 mmol), CuBr (10 mol %), ligand **A** (12 mol %), and DIPEA (2 equiv) in methanol (1.5 mL). [b]Yield referred to isolated pure **3**. [c]Enantiomeric excess of **3** was determined by chiral HPLC analysis.

reaction proceeded smoothly to afford the desired product **3ac** in 80% yield after 3 h, albeit in a rather low ee of 30%. When the temperature was lowered from room temperature to 0 °C, the enantioselectivity was increased substantially from 31% ee to 68% ee (entry 2). The ee of **3ac** was further improved to 76%, when the reaction was performed at −20 °C (entry 3). While a longer reaction time (24 h) was required to secure a high conversion rate of the starting materials. Replacing **2a** with *tert*-butyl 1-phenylprop-2-ynyl carbonate (**2b**) under similar reaction conditions led to the formation of **3ac** with results comparable to those of **2a** (entry 4). While the use of 1-phenyl-2-ynyl pivalate (**2c**) as a propargylic component resulted in a higher enantioselectivity of 83% ee (entry 5). Using less sterically crowded trimethylmethanetricarboxylate (**1b**) as a nucleophile did not enhance the reaction rate and provided results slightly inferior to those of **1a** (entry 6 vs entry 5). Increasing the steric encumbrance around the nucleophilic carbon by replacing the methyl or ethyl group with bulky *tert*-butyl or benzyl group did not help to improve the chiral induction (entries 7−9). Similar to the results reported by Nishibayashi et al.,[9] no formation of the desired product was observed when using diethyl or dimethyl malonates as reaction components in the current catalytic system. The absolute stereochemistry of **3ac** was determined by correlation after its conversion to 3-phenylpentanoic acid (see Supporting Information for details). The stereochemistry of other propargylated products could be assigned by analogy.

Substrates **1a** and **2c** were selected as model substrates to explore the effects of copper salts and the ligands on the performance of the propargylation reaction (Table 2), as the

Table 2. Survey of Copper Salts and Ligands for Propargylic Substitution of 1a with 2c[a]



entry	copper salt	ligand	time (h)	yield (%)[b]	ee (%)[c]
1	CuBr	**A**	20	91	83
2	CuCl	**A**	20	90	83
3	CuI	**A**	20	89	73
4	$Cu(CH_3CN)_4PF_6$	**A**	20	90	86
5	$Cu(CH_3CN)_4ClO_4$	**A**	20	92	82
6	$Cu(CH_3CN)_4BF_4$	**A**	20	96	90
7[d]	$Cu(OTf)_2$	**A**	48	–	–
8[d]	$Cu(acac)_2$	**A**	48	–	–
9[d]	$Cu(OAc)_2$	**A**	48	–	–
10	$Cu(CH_3CN)_4BF_4$	**B**	20	92	76
11	$Cu(CH_3CN)_4BF_4$	**C**	40	32	60
12	$Cu(CH_3CN)_4BF_4$	**D**	40	57	42
13	$Cu(CH_3CN)_4BF_4$	**E**	5	90	75
14	$Cu(CH_3CN)_4BF_4$	**F**	7	89	86
15[d]	$Cu(CH_3CN)_4BF_4$	**G**	48	–	–
16[e]	$Cu(CH_3CN)_4BF_4$	**A**	20	95	90

[a]General conditions: **1a** (0.2 mmol), **2c** (0.24 mmol), Copper salt (10 mol %), ligand (12 mol %), and DIPEA (2 equiv) in methanol (1.5 mL). [b]Yield referred to isolated pure **3ac**. [c]Enantiomeric excess of **3ac** was determined by chiral HPLC analysis. [d]No formation of **3ac** as determined by TLC. [e]General conditions, except that $Cu(CH_3CN)_4BF_4$ (5 mol %) and ligand (6 mol %) in methanol (1 mL).

combination of these two substrates (Table 1, entry 5) delivered more promising results than others. First, various copper salts were examined. All the copper(I) salts worked well to afford **3ac** in excellent yields and good to excellent ee's (entries 1−6), and $Cu(CH_3CN)_4BF_4$ proved to be the best in terms of both yield and ee (entry 6). In sharp contrast, when copper(II) salts were employed as catalyst precursors, no formation of the desired product was observed even after a much longer reaction time (entries 7−9). According to the previous reports and our own observations in copper-complex

DOI: 10.1021/acs.orglett.5b02463
Org. Lett. XXXX, XXX, XXX−XXX

catalyzed propargylation, typically both copper(I) and copper(II) salts were suitable catalyst precursors.[6,7,12] The reason why copper(II) salts failed in this study remains unclear at present and needs to be explored.

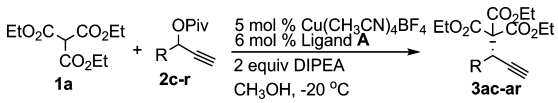
Next, other tridentate ligands **B**−**G** were examined for the propargylation reaction (entries 10−15). Ligand **B** (isopropyl-Pybox) derived from (*S*)-valine with less bulky groups as compared with ligand **A** (*sec*-butyl-Pybox) derived from (*S*)-isoleucine provided a comparable yield, albeit in a lower ee (entry 10). Ligand **C** (*tert*-butyl-Pybox) and ligand **D** (benzyl-Pybox) turned out to be less effective as compared with ligand **A** and ligand **B**, affording inferior results even after longer reaction time (entries 11, 12). Significant acceleration of the reaction rate was observed when ligand **E** (phenyl-Pybox) or ligand **F** (*iso*-butyl-Pybox) was employed, as the reaction time was shortened to 5 or 7 h respectively for complete consumption of **1a**, while the ee's in both cases were inferior to that of ligand **A** (entries 13, 14). Ligand **G** (indenyl-Pybox) was completely ineffective in this reaction (entry 15). To our delight, the loading of the $Cu(CH_3CN)_4BF_4$ and ligand **A** could be lowered to 5 and 6 mol % respectively when the reaction was performed at higher concentrations (entry 16). Attempts to further improve the outcome of this reaction by changing the base or the solvent were unsuccessful, as no better results were obtained (not shown; see Supporting Information for details).

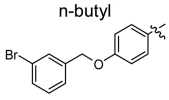
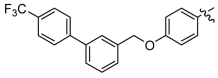
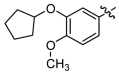
With the optimized reaction conditions in hand (Table 2, entry 16), we set out to investigate the scope of the reaction concerning different substituents at the propargylic position (Table 3). To our pleasure, phenyl-substituted propargylic substrates with either electron-donating groups, such as the methyl and methoxyl group, or electron-withdrawing groups, such as the fluoro, chloro, bromo, and trifluoromethyl group, at the *para*-site of the benzene ring all performed well to afford the propargylated products in excellent yields and ee's (entries 2−7). Substrates bearing a methoxymethoxyl (MOMO) group at the *ortho*-, *meta*-, or *para*-site of benzene ring were also examined (entries 8−10). The position of the substituents seemed to have a strong effect on the enantioselectivity of the reaction, as **2j** bearing the MOMO group at the *ortho*-position led to **3aj** with 72% ee, while *meta*-substituted **2k** and *para*-substituted **2l** delivered propargylation products with higher enantioselectivities, 91% ee and 90% ee, respectively. Replacing the MOMO group with a benzyloxy group at the *para*-site of the benzene ring led to a propargylated product with performance comparable to that of **2l** (entry 11 vs entry 10). Naphthyl substituted substrate **2n** was also fit in the current system (entry 12). According to the previous reports on asymmetric propargylation, typically an aliphatic-substituted propargylic substrate was less reactive than an aromatic one, and its propargylation reaction usually led to a low yield.[4−9] It was notable, in the current system, the reaction between aliphatic-substituted propargylic substrate **2o** and **1a** proceeded smoothly to afford **3ao** in 84% yield, albeit in rather modest 47% ee (entry 13). More advanced substrates, such as **2p**, **2q**, and **2r** (entries 14−16), all performed very well to afford propargylated products in excellent yields and high ee's. Notably, **3ap** and **3aq** were potentially useful in elaborating into AMG 837, which is a GPR40 agonist,[13] while **3ar** possessed the structural framework of a tumor necrosis factor inhibitor.[14]

With an effective protocol for eantioselective propargylic substitution of TEMT (**1a**) developed, transformation of the triester moiety of propargylation products into a malonate moiety was next explored (Table 4). We found that treating triesters **3** with NaOEt in situ generated from NaH and EtOH with THF as solvent at 0 °C provided malonates **4** in excellent yields and with excellent conservation of chiral enrichment. Thus, the present work shows that TEMT (**1a**) can act as an efficient carbon-centered nucleophile in Cu−Pybox catalyzed propargylic substitution, therefore representing a suitable surrogate for diethyl malonate.

In summary, asymmetric propargylic substitution of TEMT with various propargylic pivalates bearing a terminal alkyne moiety has been developed by employing the copper−Pybox

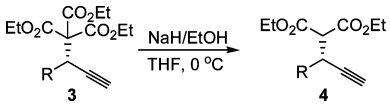
Table 3. Substrate Scope of Propargylic Pivalates[a]

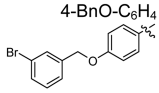
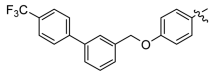
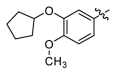


entry	R	2	3	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	**2c**	**3ac**	20	95	90
2	4-F-C_6H_4	**2d**	**3ad**	20	92	92
3	4-Cl-C_6H_4	**2e**	**3ae**	20	94	94
4	4-Br-C_6H_4	**2f**	**3af**	20	94	96
5	4-CF_3-C_6H_4	**2g**	**3ag**	30	90	93
6	4-CH_3-C_6H_4	**2h**	**3ah**	20	89	89
7	4-CH_3O-C_6H_4	**2i**	**3ai**	20	94	88
8	2-MOMO-C_6H_4	**2j**	**3aj**	30	82	72
9	3-MOMO-C_6H_4	**2k**	**3ak**	30	80	91
10	4-MOMO-C_6H_4	**2l**	**3al**	30	84	90
11	4-BnO-C_6H_4	**2m**	**3am**	30	89	87
12	1-naphthyl	**2n**	**3an**	15	94	81
13[d]	n-butyl	**2o**	**3ao**	48	84	47
14		**2p**	**3ap**	40	91	88
15		**2q**	**3aq**	40	93	89
16		**2r**	**3ar**	6	94	81

[a]See footnote e in Table 2. [b]Yield referred to isolated pure **3**. [c]Enantiomeric excess of **3** was determined by chiral HPLC analysis. [d]Ligand **E** was employed.

Table 4. Decarboxylation of Triester 3[a]



entry	R	3	ee % of 3	4	yield (%)[b]	ee % of 4[c]
1	Ph	**3ac**	90	**4ac**	95	90
2	4-F-C_6H_4	**3ad**	92	**4ad**	93	90
3	4-Cl-C_6H_4	**3ae**	94	**4ae**	96	94
4	3-MOMO-C_6H_4	**3ak**	91	**4ak**	91	90
5	4-BnO-C_6H_4	**3am**	87	**4am**	94	86
6		**3ap**	88	**4ap**	94	84
7		**3aq**	89	**4aq**	92	88
8		**3ar**	81	**4ar**	95	81

[a]General conditions: **3** (0.1 mmol), NaH (0.2 mmol), ethanol (0.2 mmol), in THF (2 mL) at 0 °C. [b]Yield referred to isolated pure **4**. [c]Enantiomeric excess of **4** was determined by chiral HPLC analysis.

DOI: 10.1021/acs.orglett.5b02463
Org. Lett. XXXX, XXX, XXX−XXX

complex as the catalyst, with excellent yields and high ee's achieved. This is the first example utilizing TEMT as the nucleophile in asymmetric catalysis. The present work shows that TEMT can act as a suitable surrogate for diethyl malonate in asymmetric propargylic substitution, as one of three ester groups in the propargylation product could be easily removed by treating with NaOEt without loss of enantiomeric enrichment. Further extension of this method to a broader range of substrates and its application in the synthesis of biologically active molecules is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02463.

General experimental conditions, NMR spectra, and HPLC analysis of the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wuxy@shu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge research support from the National Natural Science Foundation of China (Nos. 21272150 and 21072125). Dr. Hanwei Hu at Topharman is also gratefully acknowledged for helpful discussions.

■ REFERENCES

(1) For reviews on the propargylic substitution, see: (a) Ljungdahl, N.; Kann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 642. (b) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, *2009*, 6263. (c) Miyake, Y.; Uemura, S.; Nishibayashi, Y. *ChemCatChem* **2009**, *1*, 342. (d) Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914. (e) Debleds, O.; Gayon, E.; Vrancken, E.; Campagne, J.-M. *Beilstein J. Org. Chem.* **2011**, *7*, 866. (f) Nishibayashi, Y. *Synthesis* **2012**, *2012*, 489. (g) Zhang, D.-Y.; Hu, X.-P. *Tetrahedron Lett.* **2015**, *56*, 283.

(2) (a) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, *18*, 4163. (b) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.

(3) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282.

(4) (a) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715. (b) Matsuzawa, H.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2007**, *9*, 5561. (c) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488. (d) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 10498. (e) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7289. (f) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Chem. - Eur. J.* **2012**, *18*, 3321. (g) Senda, Y.; Nakajima, K.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 4060.

(5) (a) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777. (b) Detz, R. J.; Abiri, Z.; le Griel, R.; Hiemstra, H.; van Maarseveen, J. H. *Chem. - Eur. J.* **2011**, *17*, 5921.

(6) Fang, P.; Hou, X. L. *Org. Lett.* **2009**, *11*, 4612.

(7) (a) Zhang, C.; Hu, X. H.; Wang, Y. H.; Zheng, Z.; Xu, J.; Hu, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 9585. (b) Zhu, F. L.; Zou, Y.; Zhang, D. Y.; Wang, Y. H.; Hu, X. H.; Chen, S.; Xu, J.; Hu, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 1410. (c) Han, F. Z.; Zhu, F. L.; Wang, Y. H.; Zou, Y.; Hu, X. H.; Chen, S.; Hu, X. P. *Org. Lett.* **2014**, *16*, 588. (d) Zhu, F. L.; Wang, Y. H.; Zhang, D. Y.; Hu, X. H.; Chen, S.; Hou, C. J.; Xu, J.; Hu, X. P. *Adv. Synth. Catal.* **2014**, *356*, 3231. (e) Zhu, F. L.; Wang, Y. H.; Zhang, D. Y.; Xu, J.; Hu, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 10223. (f) Zhang, D. Y.; Zhu, F. L.; Wang, Y. H.; Hu, X. H.; Chen, S.; Hou, C. J.; Hu, X. P. *Chem. Commun.* **2014**, *50*, 14459. (g) Zhang, D. Y.; Shao, L.; Xu, J.; Hu, X. P. *ACS Catal.* **2015**, *5*, 5026.

(8) Shao, W.; Li, H.; Liu, C.; Liu, C. J.; You, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 7684.

(9) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 3408.

(10) For pK_a of TEMT, see: (a) Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 1177. For pK_a of Meldrum's acid, see: (b) Arnett, E. M.; Harrelson, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 809.

(11) For a review about the chemistry of methanetricarboxylic esters: Newkome, G. R.; Baker, G. R. *Org. Prep. Proced. Int.* **1986**, *18*, 117.

(12) For examples of copper-Pybox catalyzed propargylic substitution: (a) Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2014**, *50*, 7874. (b) Nakajima, K.; Shibata, M.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2015**, *137*, 2472. (c) Zhao, L.; Huang, G. X.; Guo, B. B.; Xu, L. J.; Chen, J.; Cao, W. G.; Zhao, G.; Wu, X. Y. *Org. Lett.* **2014**, *16*, 5584. Also see refs 5 and 8.

(13) (a) Akerman, M.; Houze, J.; Lin, D. C. H.; Liu, J.; Luo, J.; Medina, J. C.; Qiu, W.; Reagan, J. D.; Sharma, R.; Shuttleworth, S. J.; Sun, Y.; Zhang, J.; Zhu, L. Int. Appl. PCT, WO 2005086661, 2005. (b) Houze, J. B.; Zhu, L.; Sun, Y.; Akerman, M.; Qiu, W.; Zhang, A. J.; Sharma, R.; Schmitt, M.; Wang, Y.; Liu, J.; Liu, J.; Medina, J. C.; Reagan, J. D.; Luo, J.; Tonn, G.; Zhang, J.; Lu, J. Y.-L.; Chen, M.; Lopez, E.; Nguyen, K.; Yang, L.; Tang, L.; Tian, H.; Shuttleworth, S. J.; Lin, D. C.-H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1267.

(14) Christensen, S. B., IV; Karpinski, J. M.; Frazee, J. S. Int. Appl. PCT, WO 9703945, 1997.

DOI: 10.1021/acs.orglett.5b02463
Org. Lett. XXXX, XXX, XXX−XXX