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Highly Efficient Cu Catalyst System for the Radical Reactions of α-Bromocarbonyls

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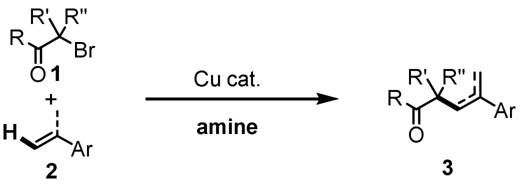
In this paper, we established highly efficient Cu-catalyzed ARGET-ATRS (atom-transfer radical substitution) of alpha-bromocarbonyls and styrenes to produce tert-alkylated styrenes. The maximum TON is up to 12000. Hünig's base was very important to regenerate active Cu^I. Moreover, Cu-catalyzed C-C cleavage reaction via S$_H$2' and intermolecular C-H cyclization of α–bromoimide were found.

Atom-transfer radical addition (ATRA) using α–bromocarbonyls is one of the most useful reactions and various modified reactions have been reported[1]. α–Bromocarbonyl compound reacts with a metal catalyst (M^n) to generate a radical species and M^{n+1} and the resulting radical reacts with olefins to generate diverse functional molecules[1]. Although transition metal complexes including Ru, Fe, Ni and Cu have been applied to the reactions as a catalyst, a large amount of catalyst loadings (10 – 30 mol%) might be limited to develop the protocol for industrial processes[2-5]. Many reports describes that high catalyst loadings are due to a generation of inactive metal species, such as Cu^{II} [1]. In this context, continuous activator regeneration (ICAR)[6] or activators regenerated by electron transfer (ARGET)[7] process has been developed as the solution to this problem, in which AIBN(α,α'-azobisisobutyronitrile), V-70(2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)) or an inorganic reductant is employed as an electron donor.

The research for the activity of a copper catalyst is one of the main streams in this area. For example, the intra- and intermolecular additions of carbon halides to olefins in the presence of a Cu catalyst and AIBN or V-70 resulted in TON's of over 10000, in which inactive Cu^{II} species is reduced to active Cu^I during the reaction[8]. The combination of UV light and those additives is also effective to increase the copper catalyst activities[9]. Cu-catalyzed intramolecular ATRA reactions by using ascorbic acid or KBH_4 achieved low catalyst loadings[10]. Immobilized Cu catalysts are also effective. For example, Cu metal embedded in siloxane gels or polymer realized recyclable reaction systems[11]. Amine reductants are another option to generate active Cu^I species from the reduction of Cu^{II} [12]. Highly efficient Cu catalyst systems for ATRA, and ATRP, whereas atom-transfer radical substitution (ATRS) have not yet been established. In this context, we envisaged to develop the reaction of α-bromocarbonyls **1** and styrenes **2** to obtain alkylated styrene products **3** with low Cu catalyst loadings in the presence of amine as an activator for Cu (Scheme 1).



Scheme 1 ARGET-ATRS.

We previously reported that atom-transfer radical addition followed by elimination reaction to give Heck like olefin product (ATRS)[13]. Similar to ATRA, the drawback of our reactions is that the large amount of catalyst (>10 mol% Cu salt) required to achieve the high yields of the products. At the first stage of this research, we re-optimized the reaction conditions in the presence of 100 ppm (0.01 mol%) of Cu catalyst (Table 1). Although the reaction did not occur under the conditions (no catalyst, no multidentate nitrogen ligand, at room temperature) (Runs 1 and 2), PMDETA, Me_6TREN and TPMA gave TONs of 2100, 3500 and 4500 (Runs 3-5). We screened various amines and found that iPr_2EtN (Hünig's base) gave the best yield with TON of 5200

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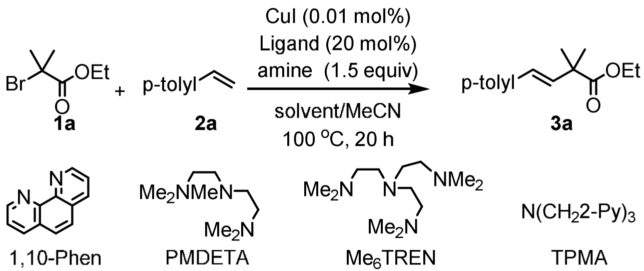
(Runs 6-9). The product **3a** was not obtained without amines, which implies that amine plays an import role for the generation of active Cu^{I} species continuously. Solvent effect is a little bit important and 1,2-dimethoxyethane gave the best yield (Run 10). When the reaction carried out with 200 and 400 ppm of CuI, 72% and 88% of **3a** with TONs of 3600 and 2200 were obtained (Runs 11 and 12).

Table 1 Optimization[a].

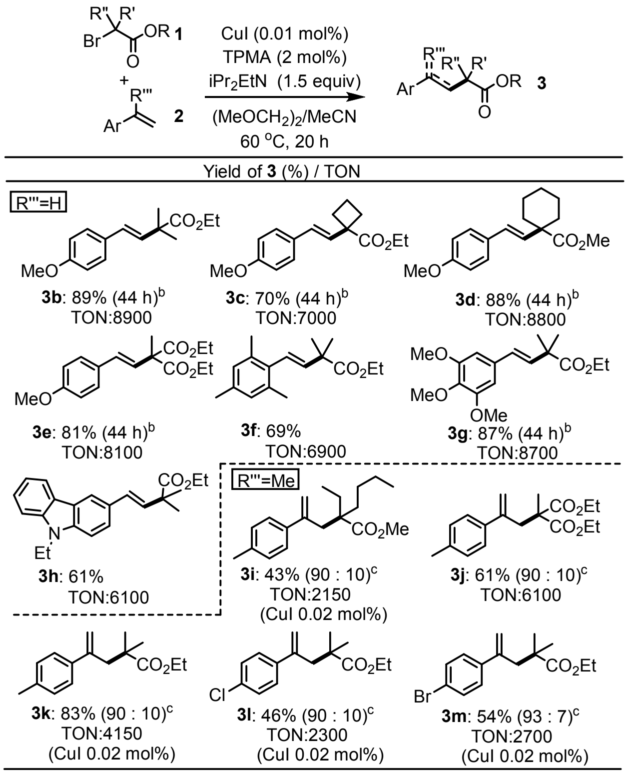


Run	Ligand	Amine	Solvent	3a (%)	TON
1	none	iPr_2NH	toluene	0	0
2	1,10-Phen (20)	iPr_2NH	toluene	0	0
3	PMDETA (20)	iPr_2NH	toluene	21	2100
4	Me_6TREN (20)	iPr_2NH	toluene	35	3500
5	TPMA (20)	iPr_2NH	toluene	45	4500
6	TPMA (2)	iPr_2NH	toluene	49	4900
7	TPMA (2)	Et_3N	toluene	42	4200
8	TPMA (2)	Hex_3N	toluene	40	4000
9	TPMA (2)	iPr_2EtN	toluene	52	5200
10	TPMA (2)	iPr_2EtN	$(MeOCH_2)_2$	55	5500
11[b]	TPMA (2)	iPr_2EtN	$(MeOCH_2)_2$	72	3600
12[c]	TPMA (2)	iPr_2EtN	$(MeOCH_2)_2$	88	2200

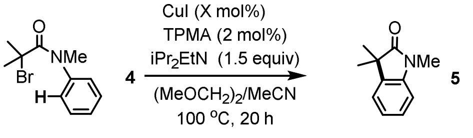
[a] All reactions were carried out at 100 ºC for 20 h with 0.01 mol% Cu salt (5 x 10^{-4} M in MeCN), Ligand (20 mol%), amine (1.2 equiv), **1a** (2.0 equiv.) and **2a** (1.0 equiv.). Yields were determined by ^{1}HNMR. The **3a** was trans. [b] 0.02 mol% CuI was used. [c] 0.04 mol% CuI was used.

Under optimal conditions, ATRS proceeded smoothly by using low catalyst loadings (Table 2). The reaction of various α–bromoesters **1** and styrene derivatives **2** to give internal alkene products (**3b-3h**) achieved TON's of up to 8900. Interestingly, the reaction of α–bromoamide **4** and **2** did not give any olefination products **3** but intramolecular C-H cyclization product **5** (oxindole derivatives) was obtained quantitatively when 200 pm of CuI was used (Scheme 2)[14]. This C-H reaction occurred in the presence of 50 ppm of CuI and the maximum TON was 25000. We also applied this reaction conditions to the reaction of α–methylstyrene derivatives **1**. As the result, typical substrates gave the corresponding allylic compounds (**3a**, **3i-3m**) in moderate to good yields with TON's of up to 6100. In this case, endo- and exo-isomers were obtained [13b]. We also examined other α–alkylstyrene possessing cumyl group **6** but the desired olefination product **3** was not obtained (Scheme 3). In this case, C-C cleavage reaction (S_H2' like reaction) occurred to produce **3l** in the yield of up to 73% with TON's of up to 3650, in which stable cumyl radical is a leaving group.

Table 2 Substrate scope[a].

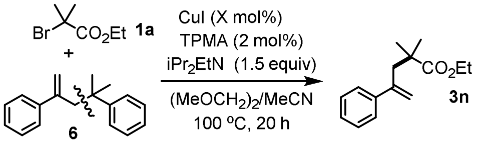


[a] All reactions were carried out in $(MeOCH_2)_2$ at 100 ºC for 20 h with 0.01 mol% CuI (5 x 10^{-4} M in MeCN), TPMA (2 mol%), iPr_2EtN (1.2 equiv), **1** (2.0 equiv.) and **2** (1.0 equiv.). Yields were isolated. The **3b-3h** were trans. [b] Reaction was carried out at 60 ºC. [c] The ratio is endo:exo.



X	Yield	TON
0.02	quant.	5000
0.01	77%	7700
0.002	50%	25000

Scheme 2 C-H cyclization.



X	Yield	TON
0.02	73%	3650
0.01	36%	3600

Scheme 3 C-C bond cleavage.

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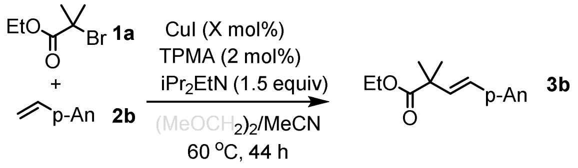
Finally, we checked the maximum TON for the reaction of **1a** and **2b** in the presence of 100, 50, 20 and 10 ppm of CuI (Table 3). Although 50 ppm of CuI gave TON of 7800 (Trun 3), better TON was obtained in the reaction with 20 ppm of CuI (TON=12000) (Run 4). The reaction was stopped when 10 ppm of CuI was employed (run 5). Additionally, when 5 mmol scale reaction was carried out in the presence of 100 ppm of CuI, 75% yield of **3b** with TON of 7500 was obtained (Run 2)[15].

Table 3 Substrate scope[a].



Run	CuI (X mol%)	**3b** (%)	TON
1	0.01	89	8900
2[b]	0.01	75	7500
3	0.005	39	7800
4	0.002	24	12000
5	0.001	0	0

[a]All reactions were carried out in $(MeOCH_2)_2$ at 60 ºC for 44 h with CuI (5 x 10^{-4} M in MeCN), TPMA (2 mol%), iPr_2EtN (1.2 equiv), **1a** (2.0 equiv.) and **2b** (1.0 equiv.). The **3b** was trans.Yields were isolated. [b]5 mmol scale.

Conclusions

In conclusion, we discovered that Hünig's base improves the catalyst activity of CuI in ARGET-ATRS. In this reaction, various alkylated styrenes **3** were obtained with TON's up to 12000. Moreover, α–bromoimide **4** gave C-H cyclization product **5** in high yield with high TON. These results are useful to carry out ATRS with the minimal amounts of cheap Cu metals. Further improvements including our original ligand design and activator for a Cu catalyst will be described in due course.

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Notes and references

1 (a) T. Pintauer, K. Matyjaszewski, *Chem. Soc. Rev.,* 2008, **37**, 1087; (b) T. Pintauer, *Eur. J. Inorg. Chem.,* 2010, 2249; (c) W. T. Eckenhoff, T. Pintauer, *Catal. Rev.: Sci. Eng.,* 2010, **52**, 1; (d) W. T. Eckenhoff, A. B. Biernesser, T. Pintauer, *Inorg. Chem.,* 2012, **51**, 11917; (e) A. J. Clark, *Eur. J. Org. Chem.,* 2016, 2231.
2 J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev*., 1994, **94**, 519.
3 K. Severin, *Curr. Org. Chem*., 2006, **10**, 217.
4 R. A. Gossage, L. A. Van De Kuil, G. Van Koten, *Acc. Chem. Res*., 1998, **31**, 423.
5 A. J. Clark, *Chem. Soc. Rev*., 2002, **31**, 1.
6 K. Matyjaszewski, W. Jakubowski, K. Min, W. Tang, J. Huang, W. A. Braunecker, N. V. Tsarevsky, *Proc. Natl. Acad. Sci. USA*, 2006, **103**, 15309.
7 (a) W. Jakubowski, K. Matyjaszewski, *Angew. Chem., Int. Ed*., 2006, **45**, 4482. (b) W. Jakubowski, K. Min, K. Matyjaszewski, *Macromolecules*, 2006, **39**, 39.
8 (a) W. T. Eckenhoff, T. Pintauer, *Inorg. Chem*., 2007, **46**, 5844; (b) W. T. Eckenhoff, S. T. Garrity, T. Pintauer, *Eur. J. Inorg. Chem.,* 2008, 563; (c) C. Ricardo, T. Pintauer, *Chem. Commun.,* 2009, 3029; (d) T. Pintauer, W. T. Eckenhoff, C. Ricardo, M. N. C. Balili, A. B. Biernesser, S. J. Noonan, M. J. W. Taylor, *Chem. Eur. J.,* 2009, **15**, 38.
9 M. N. C. Balili,T. Pintauer, *Dalton Trans.,* 2011, **40**, 3060.
10 (a) A. J. Clark, A. E. C. Collis, D. J. Fox, L. L. Halliwell, N. James, R. K. O'Reilly, H. Parekh, A. Ross, A. B. Sellars, H. Willcock, P. Wilson, *J. Org. Chem.,* 2012, **77**, 6778; (b) A. J. Clark, A. Cornia, F. Felluga, A. Gennaro, F. Ghelfi, A. A. Isse, M. C. Menziani, F. Muniz-Miranda, F. Roncaglia, D. Spinelli, *Eur. J. Org. Chem.,* 2014, 6734.
11 (a) Y. Motoyama, K. Kamo, A. Yuasa, H. Nagashima, *Chem. Commun.,* 2010, **46**, 2256. (b) A. J. Clark, J. V. Geden, S. Thom, *J. Org. Chem.,* 2006, **71**, 1471.
12 J. F. Weiss, G. Tollin, J. T. Yoke, *Inorg. Chem*., 1964, **3**, 1344.
13 (a) T. Nishikata, S. Ishikawa, *Synlett*, 2015, 716; (b) T. Nishikata, K. Nakamura, K. Itonaga, S. Ishikawa, *Org. Lett*., 2014, **16**, 5816; (c) T. Nishikata, Y. Noda, R. Fujimoto, T. Sakashita, *J. Am. Chem. Soc*., 2013, **135**, 16372. See other ATRS reactions: (d) C. Liu, S. Tang, D. Liu, J. Yuan, L. Zheng, L. Meng, A. Lei, *Angew. Chem., Int. Ed.,* **2012**, *51*, 3638; (e) K. Zhu, J. Dunne, M. P. Shaver, S. P. Thomas, *ACS Catal*., 2017, **7**, 2353; (f) X. Chen, X. Liu, J. T. Mohr, *J. Am. Chem. Soc*., 2016, **138**, 6364.
14 C. Liu, D. Liu, W. Zhang, L. Zhou, A. Lei, *Org. Lett*., 2013, **15**, 6166.

[15] We used dimethyl 2,2'-azobis(isobutyrate) instead of the Cu catalyst but no reaction occurred. This result could show that our reaction is not chain reaction.