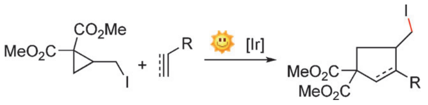
Radical chemistry! A visible-light-promoted, tin/boron-free intermolecular [3+2] atom-transfer radical cyclization reaction was developed by using iridium polyphenylpridinyl complex as the sensitizer (see scheme). 2-(Iodomethyl)cyclopropane-1,1-dicarboxylate reacted with various alkenes and alkynes to form cyclopentane and cyclopentene derivatives.



Organic Synthesis

X. Gu, X. Li, Y. Qu, Q. Yang, P. Li, Y. Yao** .... ■■■■–■■■■

Intermolecular Visible-Light Photoredox Atom-Transfer Radical [3+2]-Cyclization of 2-(Iodomethyl)cyclopropane-1,1-dicarboxylate with Alkenes and Alkynes

CHEMISTRY
A EUROPEAN JOURNAL
ChemPubSoc Europe

DOI: 10.1002/chem.201301943

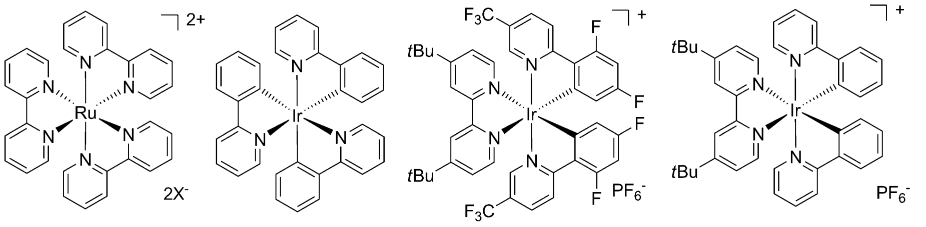
Intermolecular Visible-Light Photoredox Atom-Transfer Radical [3+2]-Cyclization of 2-(Iodomethyl)cyclopropane-1,1-dicarboxylate with Alkenes and Alkynes

Xiangyong Gu, Xiang Li, Yue Qu, Qi Yang, Pixu Li,* and Yingming Yao*[a]

Practical and innovative methods to construct five-membered rings are always of great interest to synthetic chemists. Radical cyclizations are desirable processes because of their mild conditions and high functional-group compatibility.[1] Atom-transfer radical additions or cyclizations (ATRA/ATRC) of halogenated alkanes to unsaturated carbon–carbon bonds, originally reported by Kharasch and co-workers,[2] have received considerable attention and have become a powerful synthetic methodology.[3] ATRC reactions are particularly useful in the formation of C–C bonds and the construction of cyclic frameworks.[1e,4] However, free-radical reactions, including ATRC, often employ stoichiometric hazardous radical initiators. This drawback limits their utility and applications in organic synthesis. The development of environmentally benign and practical ATRC radical initiators is, therefore, important.

Recent advances in visible-light photoredox chemistry showed improved advantages over classical radical reactions because the use of potentially hazardous radical initiators can be avoided.[5] Typical Ir- or Ru-based visible-light sensitizers used in photoredox reactions are shown in Figure 1. Many elegant visible-light-promoted intramolecular[6] and intermolecular [2+2]-,[7] [3+2]-,[8] [4+2]-,[9] and [2+2+2]-cyclization[10] reactions have recently been developed. Nonetheless, visible-light photocatalytic ATRC is still a challenge because the reductive products are preferentially formed in the quenching cycle of the catalyst, leading to the loss of halide functionality.[6c,e,11] Stephenson and co-workers reported visible-light-promoted ATRA reactions of α-halocarbonyls and polyhalogenated alkanes to alkenes by using catalysts **1** and **4**.[11b,e] However, the photoredox ATRA conditions were not applicable to ATRC because it was very substrate dependent and significant amounts of reductive product were observed with slight changes in alkene substrate.[11e] Moreover, intermolecular visible-light photoredox ATRC mediated by Ru/Ir complexes has not been reported to date.

In visible-light photoredox reactions, substrates containing activated C–X bonds, such as α-halocarbonyl compounds,[11a,b,12] polyhalogenated alkanes,[7b,13] benzyl bromides bearing strong electron-withdrawing groups,[14] and geminal halogenated sugars[15] have been used to generate radical intermediates. The use of substrates containing unactivated halogen–carbon bonds has proven very difficult because the redox potentials of the visible-light sensitizers are generally not high enough to break such C–X bonds. Breakthroughs of utilizing unactivated aryl/alkyl halide bonds in the visible-light-promoted reactions have recently been reported.[11c,d,16] We report herein a photocatalytic intermolecular ATRC reaction of unactivated alkyl iodides that occurs under nonreductive conditions, leading to the formation of highly functionalized cyclic products (Scheme 1).



1: [Ru(bpy)$_3$Cl$_2$]·6H$_2$O
2: [Ru(bpy)$_3$][PF$_6$]$_2$
3: [Ir(ppy)$_3$]
4: [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$
5: [Ir(ppy)$_2$(dtbbpy)][PF$_6$]

Figure 1. Typical Ru/Ir-based visible-light sensitizers. bpy = 2,2′-bipyridine; ppy = 2-phenylpyridine; dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

Two decades ago Curran's group reported the [3+2] ATRC reactions of allyl- or propargylmalonates with electron-rich olefins by using organotin reagents as the radical initiator.[17] The reaction was further developed by Taguchi and co-workers through a novel cyclopropane ring-opening to generate the homoallylic radical.[18] However, stoichiometric alkylborane and continuous oxygen injection were re-

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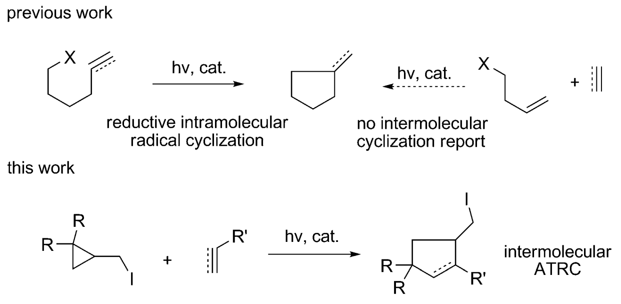
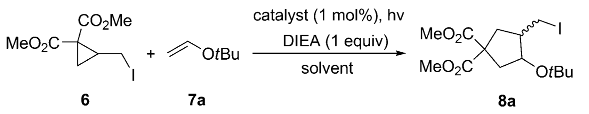
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201301943.



Scheme 1. Photoredox ATRC reactions.

quired for the reaction to proceed to completion. We initiated the investigation of the visible-light photoredox radical [3+2] ATRC reaction by using dimethyl-2-(iodomethyl) cyclopropane-1,1-dicarboxylate (**6**) and 2-methyl-2-(vinyloxy)-propane (**7a**) as the substrates, hoping to find more practical and greener reaction conditions. The results are summarized in Table 1. Among the light sensitizers investigated, the reaction with $[Ir(ppy)_3]$ (ppy = 2,2′-bipyridine) (**3**) afforded the highest yield (69%; Table 1, entries 1–4). Control experiments showed that $[Ir(ppy)_3]$, visible-light, and *N*,*N*-diisopropylethylamine (DIEA) were all essential to the reaction (entries 5–7). Interestingly, substoichiometric DIEA (0.2 equiv) afforded a 55% yield of the product, which indicated that DIEA was a catalyst in this reaction (entry 8). It was noted that the solvent has a significant effect on the reaction (entries 9–14). The reactions in polar solvents afforded higher yields (entries 10, 11, and 14). The best result was obtained by using $[Ir(ppy)_3]$ (1 mol%) as the light sensitizer and one equivalent of DIEA in a 4:1 CH_2Cl_2/H_2O biphasic solvent system. The desired cyclopentane **8a** was obtained in 85% GC yield (entry 9). Presumably, the addition of water promoted the reaction by increasing the polarity of the solvent system. In addition, the interference of I^- (E_{ox} = 0.54 V vs. SCE) in the radical initiation step was reduced by dissolving I^- into the aqueous layer.

Table 1. Optimization of intermolecular visible-light [3+2] ATRC.[a]

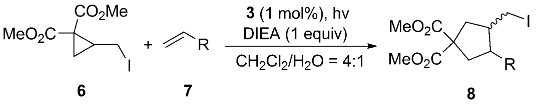


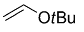
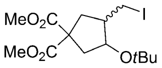
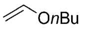
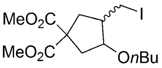
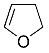
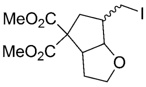
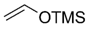
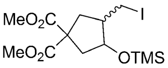
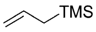
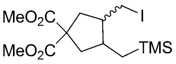
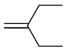
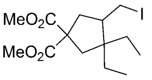
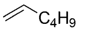
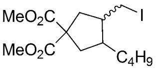
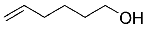
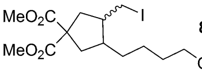
Entry	Catalyst	Solvent	Yield [%][b]
1	2	CH_2Cl_2	3[c]
2	3	CH_2Cl_2	69
3	4	CH_2Cl_2	8
4	5	CH_2Cl_2	39
5[d]	3	CH_2Cl_2	0
6	–	CH_2Cl_2	5[c]
7[e]	3	CH_2Cl_2	0
8[f]	3	CH_2Cl_2	55
9	3	CH_2Cl_2/H_2O (4:1)	85
10	3	DMF	74
11	3	DMF/H_2O (1:1)	73
12	3	toluene	1
13	3	THF	3
14	3	DMSO	73

[a] Reaction conditions: **6** (0.5 mmol), **7a** (1.0 mmol), catalyst (1 mol%), DIEA (1.0 equiv), solvent (4 mL), 14 W CFL lamp irradiation for 16 h. [b] Isolated yield. [c] GC yield, dodecane was used as the internal standard. [d] No DIEA was added. [e] The reaction was carried out in the dark. [f] 0.2 equivalents of DIEA was used.

With the optimized reaction conditions in hand, we investigated the intermolecular visible-light ATRC reaction of compound **6** with various alkenes. The results are shown in Table 2. Because of the electron-deficient nature of the radical generated from **6**, electron-rich alkenes reacted smoothly and gave satisfactory yields (Table 2, entries 1–3). Alkenes with TMS groups provided lower yields, presumably due to desilylation side reactions (entries 4 and 5). This reaction did not proceed well with less electron-rich alkenes. The reactions of 2-ethyl-1-butene (**7f**) and 1-hexene only gave 22 and 13% isolated yields, respectively (entries 6 and 7). Although the reaction of hex-5-en-1-ol afforded 18% of the cyclization product (entry 8), no protection of the hydroxyl group was necessary, which showed one of the advantages of these radical reactions.

Table 2. Intermolecular visible-light [3+2] ATRC of **6** with alkenes.[a]

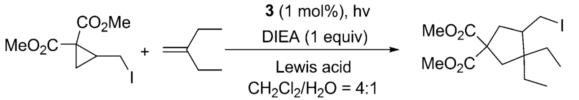


Entry	Alkene	Product	Yield [%][b]	Ratio[c]
1	 **7a**	 **8a**	85	2.6:1
2	 **7b**	 **8b**	65	1:1
3	 **7c**	 **8c**	88	27:1
4	 **7d**	 **8d**	48	1.8:1
5	 **7e**	 **8e**	47	7.8:1
6	 **7f**	 **8f**	22	–
7	 **7g**	 **8g**	13	8:1
8	 **7h**	 **8h**	18	n.d.

[a] Reaction conditions: **6** (1.0 mmol), alkene **7** (2.0 mmol), $[Ir(ppy)_3]$ (1 mol%), DIEA (1.0 equiv), CH_2Cl_2 (3.2 mL), H_2O (0.8 mL), 14 W CFL lamp irradiation for 16 h. [b] Isolated yield. [c] Ratios were determined by GC analysis.

Lewis acids have been reported to enhance the reactivity of radicals in radical reactions.[19] Coordination of Lewis acid to the ester carbonyl groups may enhance the electro-

Table 3. Screening of Lewis acids.



6 **7f** **8f**

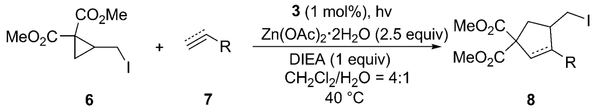
Entry	Lewis acid	Equivalent	Yield [%][a]
1	$AlCl_3$	1	n.r.
2	$BF_3{\cdot}Et_2O$	1	1
3	$TiCl_4$	1	n.r.
4	Ti(O*i*Pr)$_4$	1	2
5	$Zn(OTf)_2$	1	1
6	$ZnCl_2$	1	12
7	$MgSO_4$	1	8
8	$MgBr_2{\cdot}6\,H_2O$	1	8
9	$Mg(OAc)_2{\cdot}4\,H_2O$	1	35
10	$Yb(OTf)_2{\cdot}4\,H_2O$	1	48
11	$ZnSO_4{\cdot}2\,H_2O$	1	40
12	$Zn(OAc)_2{\cdot}2\,H_2O$	1	58
13	$Zn(OAc)_2{\cdot}2\,H_2O$	2	50
14	$Zn(OAc)_2{\cdot}2\,H_2O$	2.5	71[c]
15	$Zn(OAc)_2{\cdot}2\,H_2O$	3	56
16	$Zn(OAc)_2{\cdot}2\,H_2O$[b]	2.5	86[c]

[a] GC yield. [b] The reaction was carried out at 40 °C. [c] Isolated yield. n.r. = no reaction.

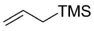
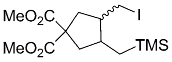
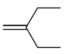
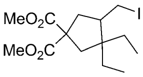
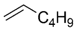
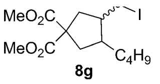
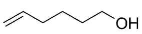
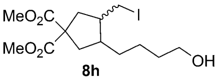
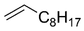
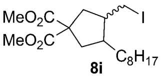
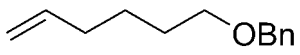
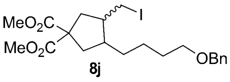
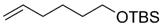
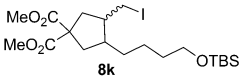
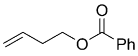
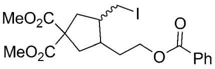
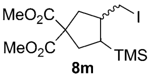
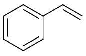
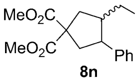
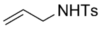
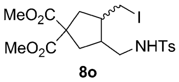
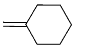
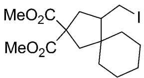
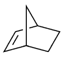
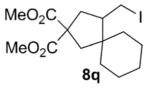
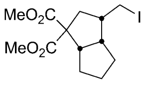
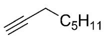
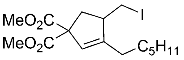
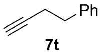
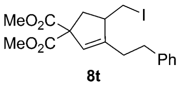
philicity of the homoallylic radical intermediate toward less electron-rich alkenes.[20] Therefore, various Lewis acids were screened in the reaction between **6** and **7f** to achieve greater substrate scope (Table 3). Lewis acids, such as $AlCl_3$, BF_3, $TiCl_4$, Ti(O*i*Pr)$_4$, and $Zn(OTf)_2$, almost completely shut down the radical cyclization (Table 3, entries 1–5). $ZnCl_2$, $MgSO_4$, and $MgBr_2$ did not help the reaction (entries 6–8). $Mg(OAc)_2$, $Yb(OTf)_2$, and $ZnSO_4$ moderately improved the reaction (entries 9–11). Among the Lewis acids screened, $Zn(OAc)_2$ gave the best results (58 %, entry 12). It was postulated that Zn^{2+} might chelate with the bidentate radical ligand and enhance its reactivity towards less electron-rich alkenes. Investigation of the amount of $Zn(OAc)_2$ used in the reaction revealed that 2.5 equivalents of $Zn(OAc)_2$ afforded the highest yield (71 %, entry 14). By raising the reaction temperature from 25 to 40 °C, cyclopentane **8f** was obtained in 86 % yield (entry 16).

With the aid of $Zn(OAc)_2$, the alkenes that did not perform well previously showed significantly enhanced reactivity. The yields of the reactions of compound **6** with alkenes **7e–h** were raised to 92, 86, 78, and 72 %, respectively (Table 4, entries 1–4). Other terminal alkenes with various functional groups, such as benzyl ether, silyl ether, and ester, were all well-tolerated (Table 4, entries 5–9). Styrene gave a moderate yield, probably due to the conjugated π-system that lowers the electron density on the double bond (entry 10). Allyl sulfonamide **7o** was not a good substrate for the reaction either (23 %, entry 11). Substrates with 1,1- and 1,2-disubstituted alkenes **7p–r** reacted with **6** and smoothly afforded the corresponding products **8p–r** in 83, 81, and 57 % yields, respectively (entries 12–14). In addition, terminal alkynes **7s** and **7t** underwent cyclization with **6** and gave cyclopentenes **8s** and **8t**, albeit in moderate yields (39 and 41 %, entries 15 and 16).

Table 4. $Zn(OAc)_2$-promoted [3+2] ATRC of **6** with alkenes and alkynes.[a]

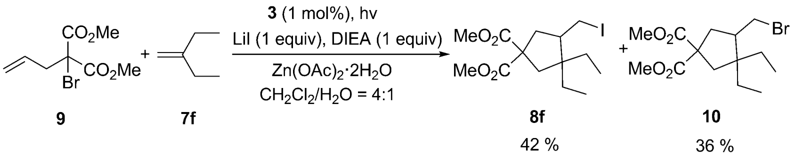


6 **7** **8**

Entry	Alkene	Product	Yield [%][b]	Ratio[c]
1	 **7e**	 **8e**	92	7.3:1
2	 **7f**	 **8f**	86	–
3	 **7g**	 **8g**	78	7.3:1
4	 **7h**	 **8h**	72	n.d.
5	 **7i**	 **8i**	75	7.0:1
6	 **7j**	 **8j**	78	6.7:1
7	 **7k**	 **8k**	89	6.3:1
8	 **7l**	 **8l**	85	7.7:1
9	 **7m**	 **8m**	68[d]	3.0:1
10	 **7n**	 **8n**	38	1.4:1
11	 **7o**	 **8o**	23[e]	n.d.
12	 **7p**	 **8p**	83	–
13	 **7q**	 **8q**	81	26.7:1
14	 **7r**	 **8r**	57[d,e]	11.8:1
15	 **7s**	 **8s**	39[f]	–
16	 **7t**	 **8t**	41[f]	–

[a] Reaction conditions: substrate **6** (1.0 mmol), alkene or alkyne **7** (2.0 mmol), [Ir(ppy)$_3$] (1 mol %), DIEA (1.0 equiv), $Zn(OAc)_2{\cdot}2\,H_2O$ (2.5 equiv), CH_2Cl_2 (3.2 mL), H_2O (0.8 mL), 14 W CFL lamp irradiation for 16 h at 40 °C. [b] Isolated yield. [c] Ratios were determined by GC analysis. [d] Reacted for 72 h. [e] 5 equivalents of alkene was used. [f] Reacted for 30 h. n.d = not determined.

For ATRA or ATRC reactions, a radical chain reaction mechanism is typically proposed. To study the radical propagation, an on/off light-switching reaction was performed. The reaction was almost stopped when the light source was turned off, and it was restarted with the reintroduction of the light source (Figure 2). This observation was confirmed by several "on/off" cycles until the reaction was completed. This experiment demonstrates that continuous radical generation under light irradiation is necessary for the reaction to proceed.



Scheme 2. Crossover ATRC.

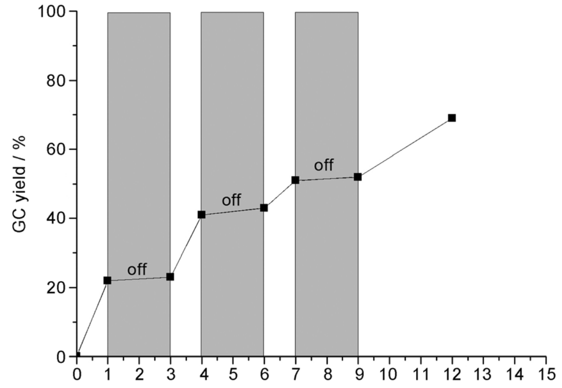


Figure 2. Time profile of reaction of **6** with **7a**. Light was switched off during the "off" periods.

The on/off light switching experiment indicates that the reaction may proceed through either a radical/polar crossover pathway or by a short-lived radical chain propagation. Because the halogen atom accepted an electron and leaves as a halide anion in the visible-light photoredox radical initiation step, we postulate that the resulting halide ion may capture the cyclopentyl carbinyl cation, as illustrated in Figure 3, path a. To confirm this hypothesis, one equivalent of LiI was added to the reaction of dimethyl 2-allyl-2-bromomalonate (**9**) with 3-methylenepentane (**7f**). Under the same conditions described above, the addition of LiI to the reaction of **9** and **7f** led to a mixture of **8f** and **10** (Scheme 2), in support of the formation of the cyclopentyl carbinyl cationic intermediate shown in Figure 3, path a. However, the interference of I^- in the radical initiation step could not be ruled out. A solid conclusion could not be drawn at this point.

As illustrated in Figure 3, $[\text{Ir(ppy)}_3]^*$ is oxidized to $[\text{Ir(ppy)}_3]^+$ ($E_{\text{red}} = -1.73$ V vs. SCE) by giving up an electron to compound **6** ($E_{\text{ox}} = \sim 0.84$ V vs. SCE, see the Supporting Information), generating homoallylic radical **11**. Radical **11** then undergoes [3+2]-cyclization with an alkene to provide radical intermediate **12**. At this stage, two pathways are possible for the conversion of **12** to the final compound **8**. In pathway a, radical **12** was oxidized by $[\text{Ir(ppy)}_3]^+$ to give primary carbon cation **13**, which reacted with the iodide anion to afford **8**. In pathway b, a short-lived radical chain propagation is proposed. Radical **12** abstracts an iodine atom from the starting material **6** to afford **8**, and radical **11** is regenerated. Pathway a is supported by our experimental observations. However, more conclusive results must be obtained to rule out pathway b.

In conclusion, a nonreductive, intermolecular visible-light photoredox [3+2] ATRC reaction was developed. In this reaction, cyclopentane/cyclopentene derivatives were formed from two structurally simpler molecules through the construction of two new C–C bonds. In our study, it was found that the homoallylic malonate radical was reactive towards electron-rich alkenes. However, the reactions with unactivated alkenes were sluggish. Zn(OAc)_2 was found to enhance the reactivity of the radical. The use of Lewis acid expanded the scope of the alkene substrates that undergo the reaction. The reaction was carried out in regular lab glassware by using a household CFL lamp. No special equipment was required. Compared to existing methods, the procedure we have described is operationally simpler and does not involve the use of stoichiometric hazardous radical initiators.

In the visible-light-promoted [3+2] ATRC reaction, unactivated iodoalkanes were successfully used as radical precursors. The nonreductive pathway is different from the reported visible-light-mediated radical cyclization reactions. Studies dedi-

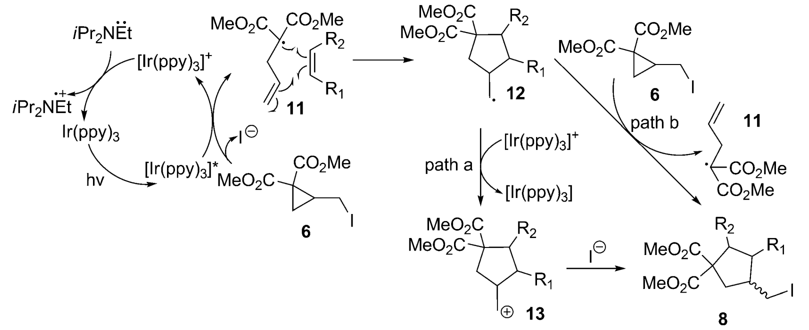


Figure 3. Possible mechanism of the intermolecular visible-light [3+2] ATRC.

cated toward the elucidation of the nonreductive course of these reactions are currently underway in our laboratory and our results will be reported in due course.

Acknowledgements

Financial support is provided by NSFC (21102097), the Specialized Research Fund for the Doctoral Program of Higher Education (20103201120006), BNLMS, and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Keywords: cyclization · Lewis acids · photochemistry · radicals · visible light

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Received: May 20, 2013