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One stone two birds: construction of polysubstituted benzenes from the same starting material and precatalyst by switching the active sites of catalyst with different additives†

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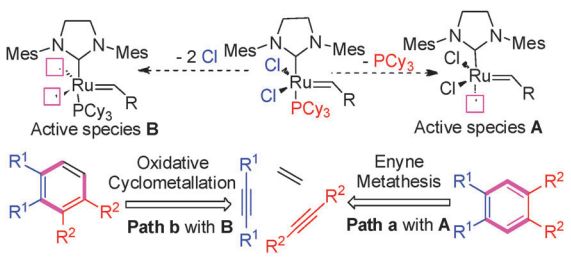
Two different tetrasubstituted benzenes were selectively constructed from the same starting materials by tuning the active sites of the Grubbs second generation catalyst (GC-II) with CuI or AgOTf as the additive.

Polyfunctionalized arene is an important structural unit in synthetic drugs and useful materials.[1] In general, two strategies have been considered to approach the construction of polysubstituted benzene. One is direct functionalization of existing benzene, for example, classic Friedel–Crafts reaction[2] and recently developed transition-metal-catalyzed direct C–H functionalizations.[3] The other one is the assembly of several small fragments to construct the benzene core structure.[4] Owing to this strategy, transition-metal-mediated [2+2+2] annulation[5] is one of the most efficient and suitable methods with high atom and step economy.[6] Herein we demonstrated a new concept to construct different polysubstituted benzenes from the same starting materials and precatalysts. The catalytic pathways to produce different products are triggered by different additives based on the understanding of the catalyst structure and our rationale design to switch the catalytic active sites (Scheme 1).



Scheme 1 Rational design to approach different products from the same materials and precatalysts by switching the active sites.

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In previous studies, the enyne metathesis followed by Diels–Alder cycloaddition and oxidation is a well-known strategy to construct the core structure of benzene derivatives.[7] With the Grubbs(II) catalyst, the understanding of mechanism indicated that the dissociation of phosphine ligand to release one coordinating site is essential to initiate the enyne metathesis and both carbene and Cl are spectator ligands to support the catalyst to keep its reactivity and stability.[8] Thus, proper additives to assist the dissociation of PCy_3 enhance the rate of metathesis (path a). On the other hand, the assembly of two alkynes and one alkene might also go through the oxidative cyclometallation followed by the annulation in the presence of stoichiometric or catalytic amount of transition metals.[9] Various catalysts can promote such transformations[10] while Ru(II) species exhibited high catalytic ability.[11] The intrinsic understanding of this pathway implied that the requirement of such an annulation by oxidative cyclometallation is two coordinating sites of Ru center, which could interact with both unsaturated species (path b). Therefore, we envisioned that different additives result in completely different active species from the same Grubbs-II catalyst with either one or two coordinating sites and trigger different catalytic pathways to produce structurally unique products (Scheme 1).

With the idea in mind, we started searching for an efficient model to prove our concept (Table 1). The treatment of diphenylacetylene (**1a**) with Grubbs-II catalyst in the absence of additives gave the mixed product of **3a** (22%) from enyne metathesis and non-metathesis product **4a** (48%) (Table 1, entry 1). It was reasoned that two competitive pathways were involved (paths a and b). In previous reports, Cu(I) salt was considered as a good additive to facilitate the dissociation of PCy_3 in different transformations.[12] To our delight, the proper amount of CuI indeed promoted both the efficiency and selectivity to produce 1,2,4,5-tetrasubstituted benzene **3a** (entry 7), which was produced through enyne metathesis/Diels–Alder annulation/dehydro-genative oxidation sequence.

Different Ag salts were further investigated to switch the pathway. Only AgOTf showed the credible effect to tune the reaction to the completely different direction and 1,2,3,4-tetrasubstituted benzene **4a** was produced from the same starting materials in good efficiency and exclusive selectivity (Table 1, entry 17). Notably, the catalyst loading was increased to 15.0 mol% to approach the high efficacy. Moreover, the reaction

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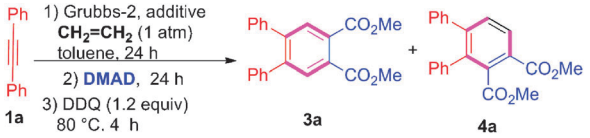
Table 1 Tunable pathway to produce different products from the same starting materials



Entry	Grubbs II (mol%)	Additive (mol%)	DMAD (equiv.)	T/ °C	**3a**[a] (%)	**4a**[a] (%)
1	5.0	—	5	80	22	48
2[b]	5.0	CuCl (5.0)	2.5	80	18	8
3[b]	5.0	CuBr (5.0)	2.5	80	16	7
4[b]	5.0	CuI (2.5)	2.5	80	59	6
5	5.0	CuI (5.0)	4.0	80	59	6
6	5.0	CuI (10.0)	5.0	80	69	<5
7	10.0	CuI (5.0)	5.0	80	85	5
8	10.0	CuI (5.0)	7.0	80	85	5
9[b]	5.0	AgCl (5.0)	2.5	80	25	5
10	5.0	AgBr (5.0)	2.5	80	18	7
11	5.0	AgOMs (5.0)	2.5	80	21	6
12	5.0	$AgBF_4$ (5.0)	5.0	80	7	25
13	5.0	AgOTf (10.0)	4.0	100	<5	42
14	10.0	AgOTf (20.0)	4.0	100	<5	58
15	10.0	AgOTf (20.0)	4.0	110	<5	62
16	15.0	AgOTf (30.0)	4.0	110	<5	55
17[c]	15.0	AgOTf (30.0)	5.0	110	<5	71
18[c,d]	15.0	AgOTf (30.0)	5.0	110	<5	75

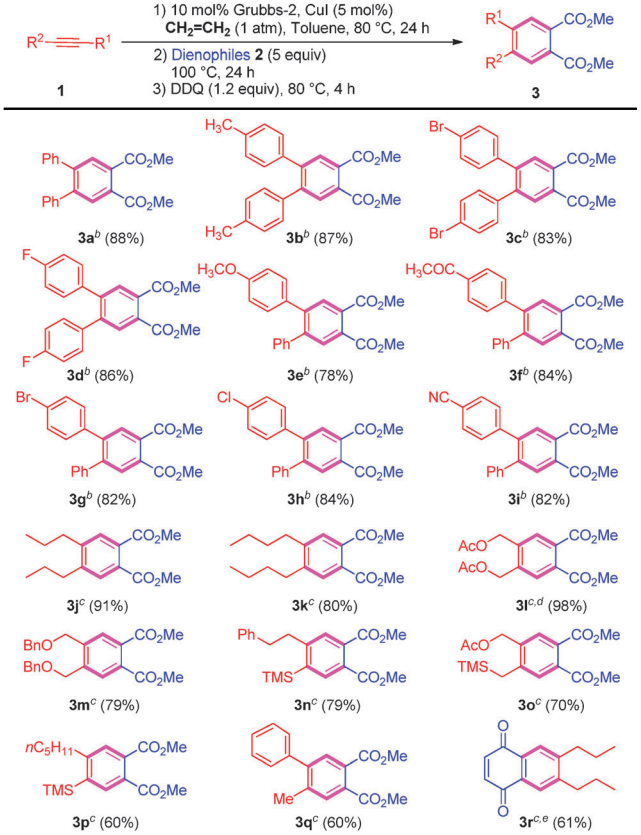
The reactions were performed in a 0.125 mmol scale of **1a** and 2.5 mL toluene was used.[a] Isolated yield. [b] 0.25 mmol **1a** and 5 mL toluene was used. [c] Step 1: reaction time 12 h. [d] 5 mL toluene was used.

temperature is also critical to promote the efficiency. Notably, the formation of a cyclometallation product catalyzed by a decomposition species of the precatalyst could not be rooted out.

Subsequently, we set out to test the different substrates for the formation of polyfunctionalized benzenes (Table 2). In the presence of CuI, various diarylacetylenes were tested and the desired products **3** were produced in good to excellent yields. Both symmetric and unsymmetric alkynes with either electron-donating group or electron-withdrawing group are compatible. The presence of halogen and O-containing groups offered a great chance for further functionalizations.[13] Notably, dialkylacetylenes also showed great reactivity by using 5 mol% Grubbs-II catalyst even in the absence of CuI. The presence of an acetoxyl/benzyloxyl group at the propargylic position produced benzylic functionalized polysubstituted benzene, which could be further utilized to construct more complicated structures and even fused ring systems.[14] Starting from TMS-substituted acetylene, the TMS group will be equipped at the formed benzene ring, which also offered the potential for further functionalization.[15] Moreover, arylalkylacetylene is also a good substrate (**3q**). Notably, 1,4-quinone is suitable as a partner, which led to the polyfunctionalized naphthalene product (**3r**).

Different diarylacetylene derivatives were also submitted to construct 1,2,3,4-tetrasubstituted benzene derivatives by tuning the reaction pathway (Table 3). Both electronic (**4a–4h**) and steric (**4i** and **4j**) factors did not affect the efficiency obviously. Similarly, C–X groups survived well (**4d–4f** and **4i**), which could be further transformed into different functionalities.[13] Heterocycles, for example thiophenyl group (**4k**), are suitable while the efficiency is slightly decreased. Similarly, 1,4-quinone as a reaction partner affords 1,4-naphthalenyldione as a product (**4l**).

Table 2 CuI-promoted enyne metathesis–DA–oxidation sequence to produce 1,2,4,5-polysubstituted benzene[a]



[a] Average isolated yields of at least two runs. [b] The reactions were carried out in the 0.125 mmol scale of **1** and 2.5 mL toluene was used. [c] The reactions were carried out in the 0.5 mmol scale of **1** with 5 mol% Grubbs-2 in the absence of CuI and 5 mL toluene was used. [d] DDQ (1.2 equiv.), 100 °C, 24 h. [e] 2 equivalent of 1,4-quinone was used.

Later on, preliminary mechanistic studies were conducted. When the 2:1 mixture of Grubbs(II) catalyst and CuI was stirred in toluene at room temperature, the *in situ* ^{31}P NMR studies indicated the slight shift of the corresponding complex adducts, which might arise from the electronic similarity of the complexes Ru-PCy_3 and Cu-PCy_3. However, the large shift of ^{31}P NMR indicated the generation of new cationic Ru(II) complexes **B** when the Grubbs(II) catalyst was treated with two equivalents of AgOTf in toluene at 90 °C for 0.5 h (Scheme 2).[16]

We made full efforts to isolate the metallocyclopentene intermediate **C** by heating diphenylacetylene (**1a**) and the active species **B** under various conditions but finally failed. Notably, the formation of **C** was indirectly proved by the subsequent insertion of DMAD, followed by reductive elimination to afford the corresponding cyclohexadiene **D** (Scheme 3).

In conclusion, we have demonstrated that the Grubbs(II) catalyst serves as a precursor for two distinct annulation reactions by a one stone, two birds strategy. By switching the catalytic active sites with CuI or AgOTf, different multi-functionalized benzene derivatives were selectively produced from the same starting materials. Not only does this rational design offer the efficient methods to construct a complicated aromatic system, but also provided a conceptually new thinking

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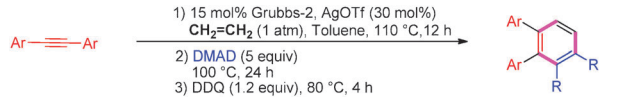
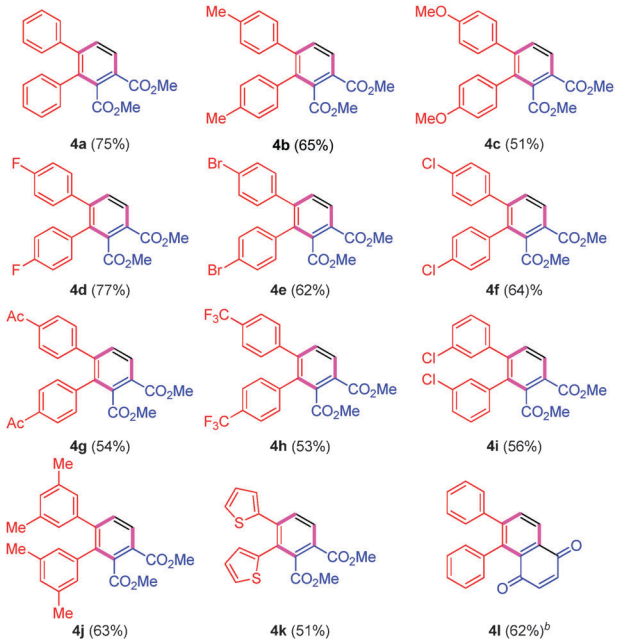
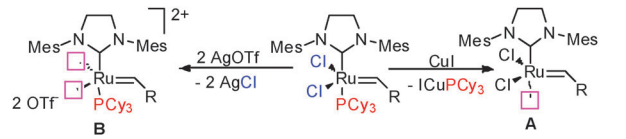
Table 3 AgOTf-promoted annulation to produce 1,2,3,4-polysubstituted benzene[a]





[a] All the reactions were carried out in the scale of 0.125 mmol of **1** and the average isolated yields of at least two runs were reported. [b] 5.0 equiv. of 1,4-quinone was used instead of DMAD.



Scheme 2 The determination of the active species **A** and **B** in the presence of either CuI or AgOTf by ^{31}P NMR.

Scheme 3 The isolation and structural determination of intermediate in path b.

about the current catalytic systems, which might lead to the new discovery based on the same precatalyst. Further studies to deliver such an efficient design to other systems are under way.

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Notes and references

1 (*a*) L. A. Thompson and J. A. Ellman, *Chem. Rev.*, 1996, **96**, 555; (*b*) L. A. Connal, R. Vestberg, C. J. Hawker and G. G. Qiao, *Macromolecules*, 2007, **40**, 7855; (*c*) R. Ballini, A. Palmieriand and L. Barboni, *Chem. Commun.*, 2008, 2975; (*d*) A. J. Inglis, S. Sinnwell, T. P. Davis, C. Barner-Kowollik and M. H. Stenzel, *Macromolecules*, 2008, **41**, 4120.

2 (*a*) G. Olah, *Friedel-Crafts and Related Reactions*, Wiley Interscience, New York, 1963, vol. I–IV; (*b*) D. E. Pearson and C. A. Buehler, *Synthesis*, 1972, 533; (*c*) J. March, *Advanced Organic Chemistry*, Wiley, NewYork, 4th edn, 1992, ch. 11, p. 501; (*d*) P. R. Chopade and J. Louie, *Adv. Synth. Catal.*, 2006, **348**, 2307.

3 (*a*) A. de Meijere and F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2004; (*b*) J. Hassan, M. Se′vignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.

4 For selected examples, see: (*a*) K. H. Dotz and P. Tomuschat, *Chem. Soc. Rev.*, 1999, **28**, 187; (*b*) H. Wang, J. Huang, W. D. Wulff and A. L. Rheingold, *J. Am. Chem. Soc.*, 2003, **125**, 8980; (*c*) Z. Xi, K. Sato, Y. Gao, J. Lu and T. Takahashi, *J. Am. Chem. Soc.*, 2003, **125**, 9568; (*d*) N. Asao, T. Nogami, S. Lee and Y. Yamamoto, *J. Am. Chem. Soc.*, 2003, **125**, 10921; (*e*) N. Asao, K. Takahashi, S. Lee, T. Kasahara and Y. Yamamoto, *J. Am. Chem. Soc.*, 2002, **124**, 12650; (*f*) N. Asao, H. Aikawa and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 7458; (*g*) P. Langer and G. Bose, *Angew. Chem., Int. Ed.*, 2003, **42**, 4033; (*h*) K. Yoshida and T. Imamoto, *J. Am. Chem. Soc.*, 2005, **127**, 10470.

5 For selected reviews, see: (*a*) K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 539; (*b*) N. E. Schore, *Chem. Rev.*, 1988, **88**, 1081; (*c*) B. M. Trost, *Science*, 1991, **254**, 1471; (*d*) M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; (*e*) D. B. Grotjahn, *Transition Metal Alkyne Complexes: Transition Metal-Catalyzed Cyclotrimerization*, in *Comprehensive Organometallic Chemistry II*, ed. G. Wilkinson, F. G. A. Stone and E. W. Abel, Pergamon, Oxford, 1995, vol. 12, p. 741; (*f*) V. Gevorgyan and Y. Yamamoto, *J. Organomet. Chem.*, 1999, **576**, 232; (*g*) S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901; (*h*) S. Kotha, E. Brahmachary and K. Lahiri, *Eur. J. Org. Chem.*, 2005, 4741.

6 (*a*) B. M. Trost, *Science*, 1991, **254**, 1471; (*b*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259.

7 (*a*) S. Kotha, S. Halder and E. Brahmachary, *Tetrahedron*, 2002, **58**, 9203; (*b*) S. Kotha, K. Mandal, S. Banerjee and S. M. Mobin, *Eur. J. Org. Chem.*, 2007, 1244; (*c*) W. A. L. Van Otterlo and C. B. De Koning, *Chem. Rev.*, 2009, **109**, 3743.

8 (*a*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18; (*b*) T. M. Trnka, J. P. Morgan, M. S. Sanford, T. E. Wilhelm, M. Scholl, T.-L. Choi, S. Ding, M. W. Day and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 2546; (*c*) S. T. Diver and A. J. Giessert, *Chem. Rev.*, 2004, **104**, 1317; (*d*) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zhu and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2008, **47**, 2489.

9 J. P. Collman and L. S. Hegedus, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, 2nd edn, 1987.

10 P. R. Chopadea and J. Louiea, *Adv. Synth. Catal.*, 2006, **348**, 2307.

11 Y. Yamamoto, T. Arakawa, R. Ogawa and K. Itoh, *J. Am. Chem. Soc.*, 2003, **125**, 12143.

12 E. L. Dias, S. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1997, **119**, 3887.

13 (*a*) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176; (*b*) D.-G. Yu, B.-J. Li and Z.-J. Shi, *Acc. Chem. Res.*, 2010, **43**, 1486; (*c*) B.-J. Li, D.-G. Yu, C.-L. Sun and Z.-J. Shi, *Chem.–Eur. J.*, 2011, **17**, 1728; (*d*) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346.

14 T. W. Green and P. G. M. Wuts, *Protective Groups In Organic Synthesis*, John Wiley and Sons, Inc., New York, 3rd edn, 1999.

15 R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, NewYork, 2nd edn, 1992.

16 For ^{31}P NMR spectrum, see ESI†.

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