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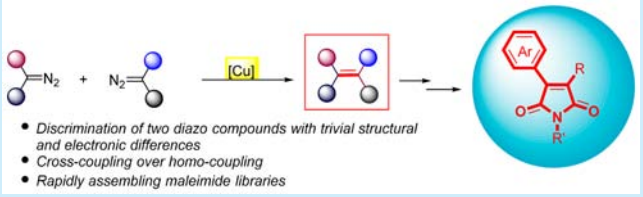
Copper-Catalyzed Diazo Cross-/Homo-Coupling toward Tetrasubstituted Olefins and Applications on the Synthesis of Maleimide Derivatives

Chenghao Zhu, Guangyang Xu, Dong Ding, Lin Qiu, and Jiangtao Sun*

School of Pharmaceutical Engineering & Life Science, and Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Changzhou University, Changzhou 213164, P. R. China

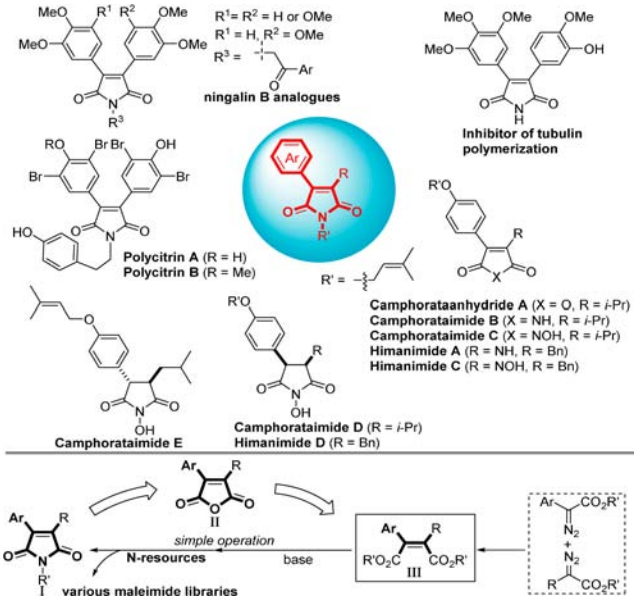
Supporting Information

ABSTRACT: A challenging selective intermolecular cross-coupling and homocoupling of aryl−aryl or aryl−alkyl diazo compounds has been accomplished via a copper system, which afforded tetrasubstituted olefins in moderate to high yields with good to excellent *Z*-selectivity. This novel methodology enables rapid synthesis of tetrasubstituted olefins, which would find broad application in accessing maleimide libraries of nature products and bioactive small molecules.



The maleimide scaffold is a key structure found in numerous nature products as well as pharmaceuticals with diverse biological activities (Scheme 1).[1] For example, camphorataanhydride A and camphorataimides B and C were found to have appreciable cytotoxic effects on Lewis lung carcinoma cell lines.[1c,g] Himanimides had the ability to inhibit the growth of bacteria and fungi.[1g] Recently, 3,4-diarylmaleimides exhibited promising P-gp-modulating activity in Pgp-overexpressing breast cancer cell lines without causing any cytotoxicity toward normal cells.[1f,h,j] Nowadays, the design, synthesis, and assessment of novel maleimides for the treatment of various diseases still receive continuous attention in drug discovery.

Scheme 1. Biologically Active 3,4-Disubstituted Maleimide Compounds and Our Strategy



Traditional approaches to construct different types of maleimides include multistep synthesis from diverse starting materials. However, those early diversification strategies are not suitable for library synthesis, and especially not ideal for high-throughput screening in drug discovery. Thus, the challenge of developing an efficient approach must be met. Obviously, a facile and straightforward way is starting from a tetrasubstituted olefin (**III**) via anhydride intermediate (**II**) by a simple operation (Scheme 1). However, to assess such an olefin is always tedious.[1] Therefore, development of an efficient approach toward rapidly assembling the olefin (**III**) is highly desirable. Upon the development of diazo transformations[2,3] and our continuous research interests in diazo chemistry,[4,9] we anticipated that the olefin (**III**) could be prepared via metal-catalyzed diazo cross-coupling, which, if feasible, would lead to the rapid discovery of bioactive maleimide molecules.

On the other hand, metal-catalyzed diazo coupling reactions were useful procedures to prepare olefins.[5,6] Rigo,[5a,b] Hodgson,[5c,d] Davies,[7] Pérez,[8] and our group[9a] successively realized the synthesis of (*Z*)-di-, (*E*)-tri-, and (*Z*)-tetrasubstituted olefins via metal-catalyzed selective diazo cross-coupling (Scheme 2). Despite these advances, there is still a rather difficult mission, namely the selective cross-coupling of two α-aryl−aryl or α-aryl−alkyl diazo compounds with trivial difference (Scheme 2d). Notably, compared with former reports, this coupling would be more challenging due to the difficulties in discrimination of two diazo compounds with minor structural difference and trivially electronic performance toward carbenoids, also in controlling the *Z*/*E* selectivity of

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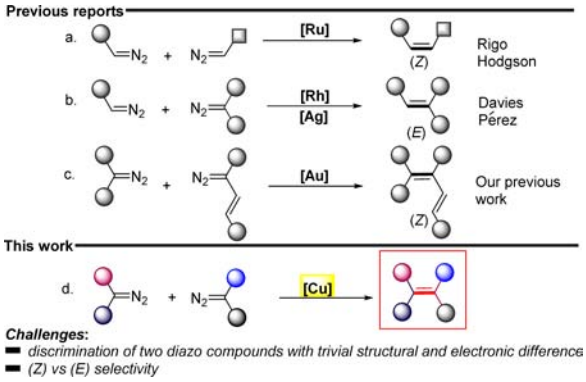
Scheme 2. Olefin Formation via Metal-Catalyzed Diazo Coupling

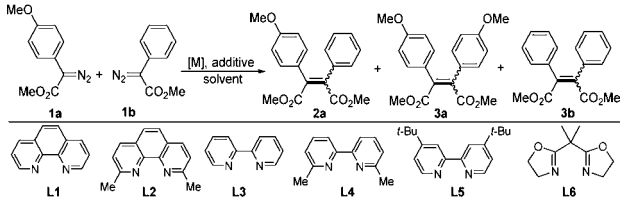


olefins. To address this issue and consistent with our systematic investigations on diazo coupling,[9] herein we report the discovery of a copper catalytic system to circumvent this hard mission, which would find broad application in synthesizing tetrasubstituted olefins as well as rapid synthesis of maleimide related pharmaceuticals.

Initially, diazoacetates **1a** and **1b** were used as model substrates to establish the optimal procedure (Table 1). Since gold complexes displayed excellent performance in cross-coupling of aryl diazoacetates and vinyl diazoacetates,[9a] we anticipated gold catalysts could also discriminate two different aryl diazoacetates toward carbenoids. To our disappointment, the use of gold catalysts only yielded a small amount of **2a** (<10% yield) in moderate *Z*/*E* selectivity (entries 1 to 5). We then attempted using copper(I) catalysts in this reaction. However, the initial results were still disappointing (see Supporting Information for details). Gratifyingly, after intensive screening, we found the combination of $CuBr_2$ and bipyridine ligands, leading to a dramatic improvement in both reactivity and selectivity (entries 6 to 10). The use of 10 mol % of $CuBr_2$ and phenanthroline (**L1**) delivered **2a** in 66% yield with excellent *Z*-selectivity (*Z*:*E* > 20:1) (entry 6). Other bipyridine ligands gave moderate selectivity, whereas a bioxazoline ligand (**L6**) led to a poor result (entry 11).

Based on the above optimizations, the substrate scope has been investigated (Scheme 3). Generally, the unsymmetrical tetrasubstituted olefins were obtained in moderate to high yields with good to excellent *Z*-selectivity. The reaction between **1a** and electron-rich phenyl diazoacetates gave the corresponding products in moderate yield and good to excellent *Z*-selectivity (**2a** to **2d**). Similar results were observed for the cross-coupling of **1a** with electron-deficient phenyl diazoacetates (**2e** to **2j**), and **2j** was isolated in 80% yield with excellent *Z*-selectivity. The reaction between two electron-deficient aryl diazoacetates also gave the unsymmetrical olefin (**2k**) in 53% yield with a 14:1 *Z*/*E* ratio. Moreover, the coupling of *ortho*-substituted phenyl diazoacetates with other aryl diazoacetates afforded the desired olefins (**2c** and **2h**) in moderate to high yields and good *Z*-selectivity (from 14:1 to >20:1). Furthermore, the reaction of aryl-alkyl diazoacetates gave the coupling products in moderate yield and good *Z*-selectivity (**2m** to **2o**). Surprisingly, the discrimination between methyl ester and ethyl ester had also been observed and provided **2p** in 48% yield favoring the *Z*-isomer.

Table 1. Optimizations[a]



entry	catalyst	additive	*t* (°C)	2a:3a:3b[b]	yield (%)[c]	*Z*/*E* of 2a[b]
1	IPrAuCl	$NaBAr_F$	25	0.2:1:1	95 (9)	3:1
2	IMesAuCl	$NaBAr_F$	25	0.2:1:1	90 (8)	3:1
3	Ph_3PAuCl	$NaBAr_F$	25	0.2:1:0.8	88 (9)	2.2:1
4	$IPrAuNTf_2$	$NaBAr_F$	25	0.2:1:1.2	92 (8)	3:1
5	IPrAuCl	$NaBAr_F$	0	0.15:1:1	86 (6)	–
6	$CuBr_2$	**L1**	80	4.6:1:0.5	87 (66)	>20:1
7	$CuBr_2$	**L2**	80	2:1:0.5	71 (40)	>20:1
8	$CuBr_2$	**L3**	80	2:1:0.8	83 (44)	10:1
9	$CuBr_2$	**L4**	80	1.2:1:0.5	65 (36)	12:1
10	$CuBr_2$	**L5**	80	2.3:1:0.5	62 (37)	8:1
11	$CuBr_2$	**L6**	80	0.4:1:1	24 (<5)	–
12	CuBr	**L1**	80	0.6:1:0.8	17 (<5)	–
13	CuI	**L1**	80	1.2:1:0.8	60 (24)	>20:1
14	CuCl	**L1**	80	1.3:1:0.6	57 (26)	>20:1
15	$Cu(OAc)_2$	**L1**	80	–	8 (–)	–
16	$Cu(OTf)_2$	**L1**	80	–	<5 (–)	–
17	$Cu(acac)_2$	**L1**	80	–	<5 (–)	–

[a]For gold catalysis: To a mixture of gold complex (0.01 mmol, 1 mol %), $NaBAr_F$ (1 mol %) in CH_2Cl_2 (2 mL) was added a solution of **1a** and **1b** (1 mmol each) in 3 mL of CH_2Cl_2 via an automatic syringe pump in 1 h. For copper catalysis: To a mixture of copper complex with an additive (0.1 mmol each, 10 mol %) in MeCN (2 mL) was added a solution of **1a** and **1b** (1 mmol each) in 3 mL of MeCN via an automatic syringe pump over 1.5 h at 80 °C and stirred for another 0.5 h. [b]Determined by ^1H NMR analysis. [c]Combined yield. Isolated yield of **2a** in parentheses.

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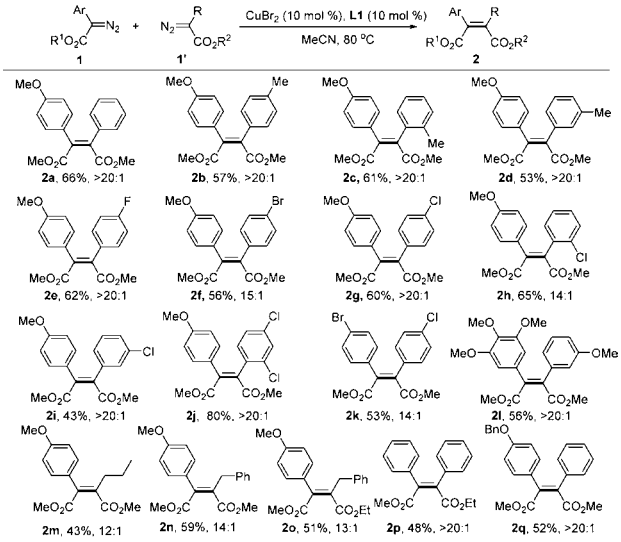
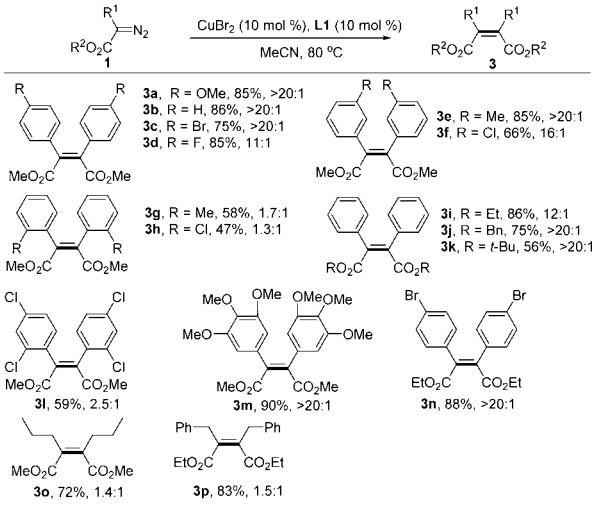
Scheme 3. Substrate Scope[a,b]



[a]Reaction conditions: a solution of diazo **1** and **1′** (1 mmol each) in 3 mL of MeCN was added to a mixture of $CuBr_2$/**L1** (0.1 mmol each, 10 mol %) in 2 mL of MeCN via an automatic syringe bump over 1 h at 80 °C and continued to be stirred for another 1 h. [b]Isolated yield of single isomer. *Z*/*E* ratios were determined by ^{1}H NMR analysis.

As the symmetrical bis-carbonyl olefins are also important precursors in the synthesis of naturally occurring maleimides and bioactive leading pharmaceuticals, we next investigated the homocoupling of diazo compounds (Scheme 4). The

Scheme 4. Copper-Catalyzed Homo-Coupling of Diazoacetates[a,b]

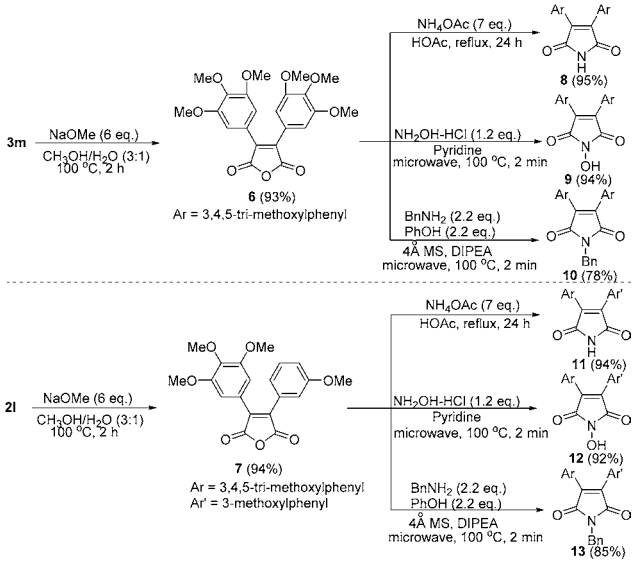


[a]Reaction conditions: a mixture of $CuBr_2$ (10 mol %), **L1** (10 mol %), and diazo **1** (1 mmol) in MeCN (5 mL) was heated to 80 °C for 2 h under nitrogen. [b]Isolated yield of single isomer. Combined yield for **3o** and **3p**. *Z*/*E* ratios were determined by ^{1}H NMR analysis.

substituent was first evaluated, and we found that for *para*- or *meta*-substituted phenyl diazoaceates, no apparent tendency was observed (**3a** to **3d**). For *ortho*-substituted phenyl diazoacetates, the corresponding alkenes were obtained in lower selectivity (**3g** to **3h**). The 2,4-dichlorophenyl diazoacetate gave the *cis* product (**3l**) in 59% yield and the *trans*-isomer **3l′** in 24% yield (the configuration was confirmed by X-ray analysis).[10] Comparatively, the methyl and ethyl ester diazoacetates gave a higher yield than the benzyl and *tert*-butyl ester (**3b**, **3i** to **3j**, **3k**). The alkyl diazoacetates were also tolerated in this reaction, but the olefins were obtained in lower selectivity (**3o** and **3p**).

With this protocol in hand, we next investigated its application in maleimide libraries synthesis (Scheme 5). The

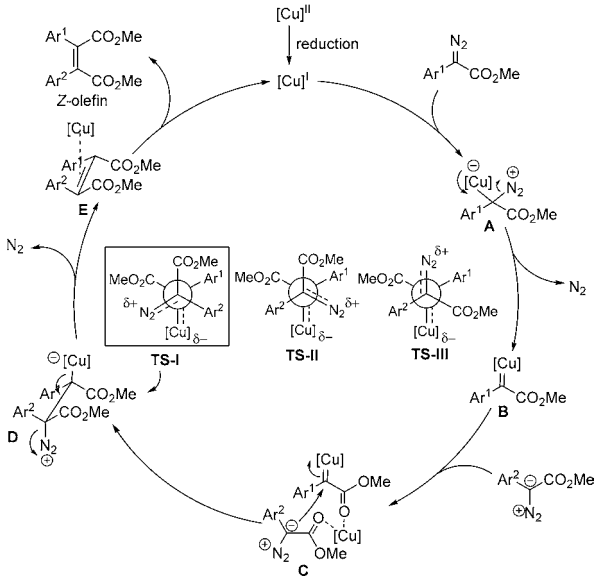
Scheme 5. Applications on Maleimide Synthesis



homocoupling of diazo **4** and cross-coupling with diazo **5** yielded olefins **3m** (90% yield) and **2l** (56% yield) respectively. Then treatment of the olefins with NaOMe provided anhydride intermediates **6** and **7** in almost quantitative yield. Next, the presence of different N-resources, such as NH_4OAc, NH_2OH·HCl, and benzylamine under mild conditions (for details, see Supporting Information), led to different 3,4-*di*-substituted maleimides **8**, **9**, **10**, **11**, **12**, and **13** in high isolated yield.

A plausible reaction mechanism is proposed in Scheme 6. Initially, the Cu^{II} complex was reduced in situ to active Cu^{I}

Scheme 6. Proposed Reaction Mechanism



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species by diazo compounds.[11] Then Cu^{I}-catalyzed cross-coupling initiated, whereas the trivial electronic difference between two diazo compounds made them play different roles. The reaction of Cu^{I} with a relatively active diazo compound delivers ylide **A**, which by releasing one molecule of nitrogen generates active copper-carbene **B**. Then **B** underwent attack by another diazo compound with stronger nucleophilicity to produce intermediate **D**. Extrusion of another molecule of nitrogen affords intermediate **E**, which rapidly releases the olefin product and regenerates the active Cu^{I} species. For the preferred *Z*-selectivity of the olefins, a possible explanation is described. During the cross-coupling process, three possible different transition states could exist. Experimental observations indicated that **TS-I** might be the most stable over **TS-II** and **TS-III**, which led to the formation of **D**. As a result, the *Z*-product formed dominantly.

In summary, we have established an efficient protocol to overcome the cross-coupling of diazo compounds with both trivial structural and electronic differences. The synthesis of unsymmetrical as well as symmetrical tetrasubstituted olefins has been achieved via a copper catalytic system under mild reaction conditions. Furthermore, we presented here a facile and straightforward way to rapidly assemble maleimide libraries. We anticipated this methodology would find broad application in screening for potential bioactive small maleimide molecules in drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02037.

Experimental procedures along with characterizing data and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jtsun08@gmail.com; jtsun@cczu.edu.cn.

Notes

The authors declare no competing financial interest.

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(10) CCDC 1412051 (**3l′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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