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Copper-Catalyzed Double *N*-Alkenylation of Amides: An Efficient Synthesis of Di- or Trisubstituted *N*-Acylpyrroles

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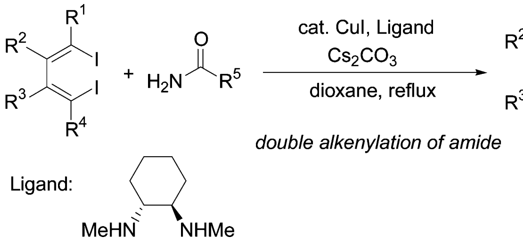

An efficient copper-catalyzed double alkenylation of amides with (1*Z*,3*Z*)-1,4-diiodo-1,3-dienes is reported for the first time. The reactions proceed to afford di- or trisubstituted *N*-acylpyrroles in good to excellent yields using CuI as the catalyst, Cs_2CO_3 as the base, and *rac-trans-N*,*N*′-dimethylcyclohexane-1,2-diamine as the ligand.

Pyrrole rings constitute an important class of heterocyclic compounds,[1] which represent not only useful building blocks in the synthesis of natural products but also key structural units in compounds that exhibit remarkable pharmacological activities.[2,3] They have also found broad applications in the field of material science.[4] As a consequence, much attention has been paid to the development of efficient methodologies for their preparation. The known methods for the construction of the pyrrole rings proceed either by traditional methods via various types of cycloaddition or cycloisomerization of acyclic precursors[5] or by transition-metal-catalyzed reactions.[6] There were also reports concerning the preparation of acylpyrroles by double condensation with amides.[7] In the past few years, copper-catalyzed aryl C−X bond (X = N, O, S, etc.) formation reactions through coupling between aryl halides and heterocentered nucleophiles has drawn considerable attention,[8] which provides an excellent complement to the Pd-catalyzed reactions. More recently, this methodology was successfully extended to the synthesis of allenamides,[8g] enamides,[9] and lactams[8h] by coupling of amides with allenyl halides, vinyl halides, and iodoenamides via intramolecular vinylation, respectively. It could be envisioned that if a tandem vinylation could proceed between an amide and a dienyl dihalide, it might provide a straightforward route for the synthesis of pyrroles with various substitutes. A palladium-catalyzed tandem alkenyl and aryl-C−N bond formation was reported by Willis[10] and double N-arylation of amines by Nozaki.[11] A number of copper-catalyzed aryl-C−N bond formation has been reported. Reports concerning alkenyl-C−N bond formation are also beginning to appear.[8h,9,12] However, no examples of a copper-catalyzed

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[1] For reviews, see: (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 207. (b) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*; Blackwell Science: Oxford, UK, 2000.

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[5] For reviews, see: (a) Gossauer, A. Pyrrole. In *Houben-Weyl*; Thieme: Stuttgart, 1994; E6a/1, p 556. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2849. (c) Tarasova, O. A.; Nedolya, N. A.; Vvedensky, V. Yu.; Brandsma, L.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 7241.

[6] For recent examples, see: (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853. (c) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957. (d) Shen, H.-C.; Li, C.-W.; Liu, R.-S. *Tetrahedron Lett.* **2004**, *45*, 9245. (e) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (f) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (g) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (h) Alcaide, B.; Almendros, P.; Redondo, M. C. *Chem. Commun.* **2006**, 2616.

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[8] For reviews, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. For selected papers, see: (c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (d) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475. (e) Ley, S.; Thomas, A. W.; *Angew. Chem., Int.* Ed. **2003**, *42*, 5400. (f) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (g) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (h) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (i) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781. (j)Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, *69*, 915. (k) Klapars, A.; Paris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (l) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (m) Cristau, H.-J.; Cellier, P. P.; Spimdler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695. (n) Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, 778.

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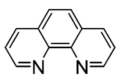
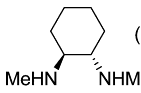
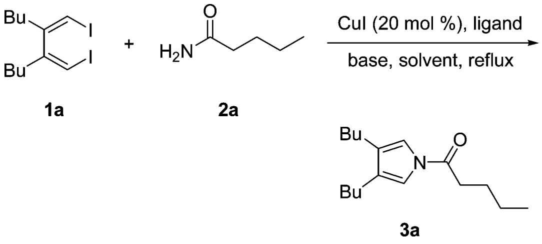
TABLE 1. Optimization of Reaction Conditions for the Formation of 3a

entry	ligand (20 mol %))	CuX (20 mol %)	base (2 equiv)	temp (°C)	yield (%)[a]
1	2,2′-bipyridine	CuI	Cs_2CO_3	100	20
2	ethane-1,2-diol	CuI	Cs_2CO_3	100	54
3	L-proline	CuI	Cs_2CO_3	100	27
4		CuI	Cs_2CO_3	100	43
5	 (**L1**)	CuI	Cs_2CO_3	100	98
6	none	CuI	Cs_2CO_3	100	15
7	**L1**	CuI	K_2CO_3	100	28
8	**L1**	CuI	K_3PO_4	100	25
9	**L1**	CuI	KOH	100	45
10	**L1**	CuI	Cs_2CO_3	110[b]	95
11	**L1**	CuI[c]	Cs_2CO_3	100	65
12	**L1**	CuI	Cs_2CO_3	80	6
13	**L1**	CuCN	Cs_2CO_3	100	76
14	**L1**	CuCl	Cs_2CO_3	100	76
15	**L1**	CuBr	Cs_2CO_3	100	63

[a] Yields were determined by GC after hydrolysis. All reactions were done for 24 h. Unless noted, all the reactions were carried out in 1,4-dioxane. [b] Toluene was used as solvent. [c] 10 mol % CuI was used.

double alkenyl-C−N bond formation toward pyrroles have been reported, to the best of our knowledge. Herein we would like to describe a copper-catalyzed tandem double alkenyl-C−N bond formation by the reaction of (1*Z*,3*Z*)-1,4-diiodo-1,3-dienes with amides.

The requisite 1,4-diiodo-1,3-dienes **1** could be conveniently synthesized in high yields through iodination of zirconacyclopentadienes followed by desilylation according to the reported method.[13] We began our investigation with (1*Z*,3*Z*)-2,3-dibutyl-1,4-diiodo-1,3-butadiene **1a**. The reaction of **1a** with valeramide **2a** was selected as the prototypical case to screen the experimental conditions (eq 1). It was demonstrated that certain copper ligands play important roles for rate accelerations in the coupling reactions. These ligands are thought to increase catalyst solubility and stability and to prevent aggregation of the metal. We first carried out ligand screen using CuI (20 mol %) as the catalyst and Cs_2CO_3 (2 equiv) as the base in dioxane at refluxing temperature. The results are summarized in Table 1. Five commercially available ligands were evaluated for the coupling reaction, and among them, the ligand of *rac-trans-N*,*N*′-dimethylcyclohexane-1,2-diamine (**L1**) gave the most promising results. Thus, heating a mixture of diiodide **1a** and amide **2a** together with CuI catalyst in the presence of 20 mol % **L1** in dioxane at 100 °C afforded the expected pyrrole **3a** in 98% yield (Table 1, entry 5). When 10 mol % CuI was used, the yield was decreased to 65% (Table 1, entry 11). The yield was rather low under ligandless condition (Table 1, entry 6). Switching to other bases such as K_2CO_3, K_3PO_4, and KOH afforded lower yields of the product (entries 7−9). Other copper salts such as CuCN, CuCl, and CuBr gave the desired product in 76%, 76%, and 63% yield, respectively (Table 1, entries 13−15). When the solvent was changed to toluene, the product yield was similar to that of dioxane (entry 10). It was clear that the optimized reaction condition was to use 20 mol % CuI in combination of 20 mol % *rac-trans-N*,*N*′-dimethylcyclohexane-1,2-diamine (**L1**) as the ligand, Cs_2CO_3 as the base, and dioxane as the solvent.



(1)

Having established an effective catalytic system for the coupling reactions, we next synthesized a variety of diiodo dienes[13] to explore the scope of double alkenylation under the optimized conditions. The representative results are shown in Table 2. The reaction was applicable to various amides and dienyl diiodo compounds. Coupling of **1a** with 2-phenylacetamide **2b** gave the corresponding pyrrole derivative **3b** in 95% GC yield (73% isolated yield) (Table 2, entry 2). The aryl amide of 4-methylbenzamide **2c** reacted with **1a** to produce **3c** in 80% GC yield (68% isolated yield) (Table 2, entry 3). Likewise, the coupling of **1a** with 4-aminobenzamide **2d** furnished the expected pyrrole **3d** in 92% GC yield (71% isolated yield), in which the NH_2 group was well tolerated during the reaction (entry 4). When 2,3-diphenyl-substituted dienyl diiodide **1b** was employed, the reaction with benzyl amide was completed within 4 h to give the desired product **3f** in 48% isolated yield (entry 6), along with 24% deacylation product 3,4-diphenyl-1*H*-pyrrole[14] (**4a**). To our delight, the crystal of **3f** was suitable for single crystal analysis, and its structure was fully characterized by X-ray diffraction analysis. Interestingly, when **1b** reacted with 2 equiv of benzamide **2e** for 20 h, the product of **4a** was obtained in 95% isolated yield as the only pyrrole product; *N*-benzoylbenzamide[15] was isolated in 51% yield (entry 7). This result indicated that the acyl-C−N bond of the initial formed pyrrole was cleaved during the reaction. It might due to the delocalization of the nitrogen lone pair into the pyrrole ring of the pyrrole amide. The reduced electrondensity on the *N*-acylpyrrole carbonyl favors nucleophilic attack. In order to make an insight into this reaction, we stopped the reaction at 3 h, and the corresponding acyl pyrrole **3g** was obtained in 54% yield along with **4a** (22%) and *N*-benzoylbenzamide (30%) (entry 8). This reaction provides a useful method for synthesis of pyrroles with two aryl groups on adjacent positions, which frequently display interesting biological and pharmacological properties.[2d]

When a diiodide fused with a six-membered ring of **1c** was used, the reaction smoothly occurred to afford bicyclic pyrrole **3h** in 89% yield (entry 9). Interestingly, this method is also effective for trisubstituted dienyl diiodide compounds. The reaction of (1*Z*,3*Z*)-2-butyl-1,4-diiodo-3-propylhepta-1,3-diene

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(13) (a) Xi, Z.; Song, Z.; Liu, G.; Liu, X.; Takahashi, T. *J. Org. Chem.* **2006**, *71*, 3154. (b) Xi, Z.; Liu, X.; Lu, J.; Bao, F.; Fan, H.; Li, Z.; Takahashi, T. *J. Org. Chem.* **2004**, *69*, 8547. (c) Takahashi, T.; Kondakov, D. Y.; Xi, Z.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *117*, 5871. (d)Takahashi, T.; Sun, W.; Xi, C.; Ubayama, H.; Xi, Z. *Tetrahedron* **1998**, *54*, 715. (e) Ubayama, H.; Sun, W.; Xi, Z.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1998**, 1931.

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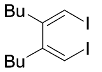
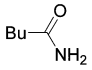
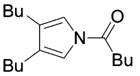
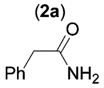
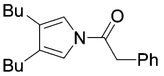
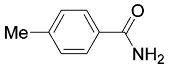
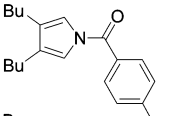
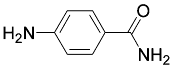
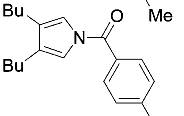
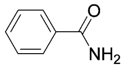
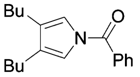
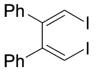
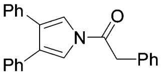
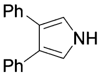
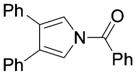
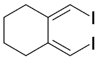
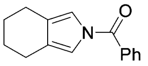
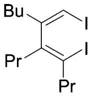
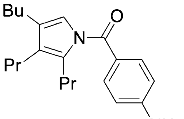
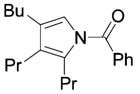
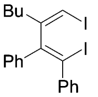
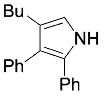
(15) Etler, M. C.; Reutzel, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 2586.

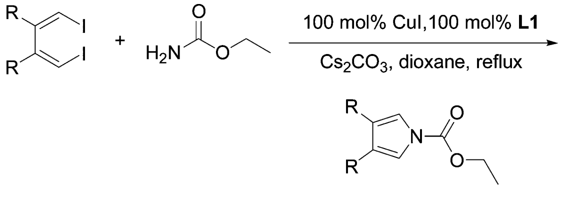
TABLE 2. Preparation of Pyrroles from Amides and Dienyl Diiodides

Entry	Dienyl diiodide	Amide	Time (h)	Product		Yield[a]
1	 (**1a**)	 (**2a**)	24		**3a**	95
2	(**1a**)	 (**2b**)	18		**3b**	73
3	(**1a**)	 (**2c**)	24		**3c**	68
4	(**1a**)	 (**2d**)	18		**3d**	71
5	(**1a**)	 (**2e**)	24		**3e**	54
6	 (**1b**)	**2b**	4		**3f**	48[b]
7	(**1b**)	**2e**	20		**4a**	95[c]
8	(**1b**)	**2e**	3		**3g**	54[d]
9	 (**1c**)	**2e**	20		**3h**	89
10	 (**1d**)	**2d**	24		**3i**	70
11	(**1d**)	**2e**	24		**3j**	54
12	 (**1e**)	**2e**	20		**4b**	32

[a] Isolated yields. [b] 3,4-Diphenyl-1*H*-pyrrole **4a** was obtained in 24% yield. [c] 2 equiv of **2e** was used; *N*-benzoylbenzamide was isolated in 51% yield. [d] **4a** and *N*-benzoylbenzamide were isolated in 22% and 30% yields, respectively.

(**1d**) and amide **2d** led to the formation of **3i** in 70% isolated yield (entry 10). The substrate of **1d** also reacted with benzamide to give the trisubstituted acyl pyrrole **3j** in moderated yield (entry 11). However, the diiodide **1e** bearing a phenyl group at C1 reacted with **2e** to give the pyrrole **4b** in only 32% isolated yield after 20 h (entry 12). It should be noted when a tetrasubstituted dienyl diiodide such as (3*Z*,5*Z*)-4,5-diethyl-3,6-diiodoocta-3,5-diene was treated with **2e** under the optimized reaction condition, no coupling product was observed.

The scope of this reaction was further examined by applying the optimized conditions to carbamate. Treatment of dienyl diiodide **1a** with ethyl carbamate using a catalytic amount (20%) of CuI resulted in the formation of **3k** only in 20% yield. Reasonable yield (68%) was obtained when 1.0 equiv of ligand and 1.0 equiv of CuI was employed (eq 2).



(2)

3k: R = Bu, 68%
3l: R = Ph, 80%

In summary, we have reported the first example of double *N*-alkenylation of amides and carbamate with dienyl diiodides. This methodology provided a facile route for the synthesis of substituted pyrroles. Further application of the system to the synthesis of various heterocycles is under progress.

Experimental Section

Typical Procedure for the Formation of Pyrroles. A 20 mL Schlenk tube was charged with valeramide (101 mg, 1.0 mmol), CuI (38 mg, 0.2 mmol), and Cs_2CO_3 (652 mg, 2 mmol). After that, 8 mL of 1,4-dioxane was added, followed by *rac-trans-N*,*N*′-dimethylcyclohexane-1,2-diamine (0.032 mL, 0.2 mmol) and (1*Z*,3*Z*)-2,3-dibutyl-1,4-diiodo-1,3-butadiene **1a** (418 mg, 1.0 mmol). The reaction mixture was heated to 100 °C for 24 h and then cooled down to room temperature. The mixture was quenched with aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo, and the residue was purified by chromatography on silica gel to afford 250 mg (95%) pyrrole derivative **3a** as a light-yellow oil. GC yield: 98%. **1-(3,4-Dibutylpyrrol-1-yl)pentan-1-one** (**3a**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, $J = 7.5$ Hz, 6H), 0.88 (t, $J = 7.2$ Hz, 3H), 1.25−1.38 (m, 6H), 1.42−1.52 (m, 4H), 1.61−1.71 (m, 2H), 2.28 (t, $J = 8.1$ Hz, 4H), 2.66 (t, $J = 7.8$ Hz, 2H), 6.93 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.8, 13.9, 22.3, 22.6, 24.9, 26.8, 31.5, 33.9, 115.5, 128.8, 170.0; HRMS (EI) calcd for $C_{17}H_{29}NO$ 263.2249, found 263.2235.

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Supporting Information Available: Experimental details and characterization data of compounds **3b**−**l**, **4a**, **4b** and crystallographic data of **3f** in CIF format; copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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