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Copper-Catalyzed Stereospecific N-Allenylations of Amides. Syntheses of Optically Enriched Chiral Allenamides

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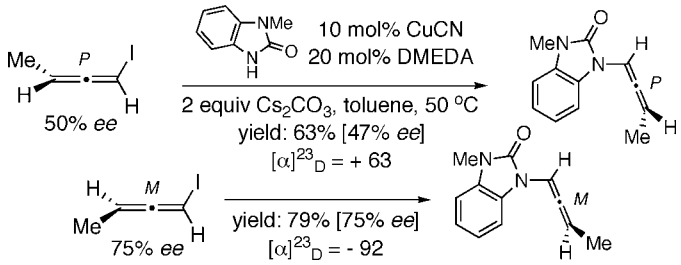
ABSTRACT



Syntheses of chiral allenamides via a stereospecific amidation of optically enriched allenyl iodides using catalytic copper(I) salt and *N,N′*-dimethylethylene-diamine are described here.

Metal-catalyzed aminations and amidations of halo arenes and alkenes have emerged in the past decade to provide a powerful method for constructing anilines or anilides and enamines or enamides.[1−5] Amidations of 1-halo alkynes were achieved recently.[6−10] While these former processes represent a cross-coupling of an sp^2-hybridized carbon, the latter involves sp-hybridized carbons, leading to an atom-economical synthesis of ynamides [Scheme 1].[11] Intriguingly, what has not been explored[12] is the amidation of allenyl halide. Although this amidative cross-coupling resembles amidations of halo alkenes, it should (1) lead to an excellent synthetic entry to allenamides,[13−15] which have become attractive synthetic building blocks,[13,16,17] and (2) provide a unique opportunity to examine the stereoselectivity issue, which has not been possible or relevant in any of the existing investigations. Recently, Trost[12] elegantly demonstrated the feasibility

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(10) For an earlier documentation of copper-promoted coupling of amide with alkyne, see: Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A. *Tetrahedron Lett.* **1985**, *26*, 4141.

(11) For reviews on ynamides, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455.

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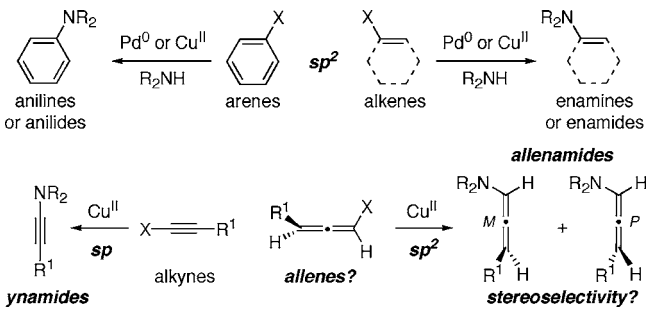
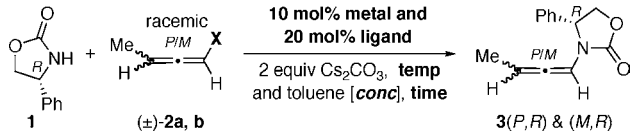
Scheme 1



of this amidative process using catalytic copper salts. Our efforts have been focused on the stereoselectivity issue. We report here a copper-catalyzed stereospecific N-allenylation of amides.

Our work commenced prior to our knowledge of Trost's recent report,[12] and thus, given lack of precedents at the time, we first carefully screened various metal catalysts mainly with palladium and copper and various ligands mostly with phosphines, 1,10-phenanthroline, and *N*,*N*-dimethylethylenediamine [DMEDA]. These results are summarized in Table 1 specifically using Evans' chiral oxazolidinone **1** and racemic allenyl halides **2a/b**. In general, allenyl iodide **2b** [entries 4−12] worked much better than bromide **2a** [entries

Table 1.



entry	metal	ligand	halide	X	concn[a] (M)	temp (°C)	time (h)	yield (%)[b]
1	$Pd[PPh_3]_4$	PR_3[c]	(±)-**2a**	Br	0.10	150	8	nd
2	$CuSO_4$	1,10-phen[d]	(±)-**2a**	Br	0.10	100	8	nd
3	CuI	1,10-phen	(±)-**2a**	Br	0.10	50	12	nd
4	CuI	1,10-phen	(±)-**2b**	I	0.15	50	8	16
5	CuI	1,10-phen	(±)-**2b**	I	0.10	110	4	nd
6	CuI	DMEDA[d]	(±)-**2b**	I	0.15	50	4	65
7	$CuSO_4$	DMEDA	(±)-**2b**	I	0.15	50	4	45
8	$CuSO_4$	1,10-phen	(±)-**2b**	I	0.15	50	18	nd
9	CuCN	DMEDA	(±)-**2b**	I	0.15	50	4	64
10	CuCN	1,10-phen	(±)-**2b**	I	0.15	50	4	55
11	CuCN	DMEDA	(±)-**2b**	I	0.075	50	18	69
12	CuCN	DMEDA	(±)-**2b**	I	0.075	rt	18	58

[a] Concentration of **2**. [b] Isolated yields; nd: not determined. [c] R = *o*-tolyl or *c*-hex. [d] 1,10-Phen: 1,10-phenanthroline. DMEDA: *N*,*N*′-dimethylethylenediamine

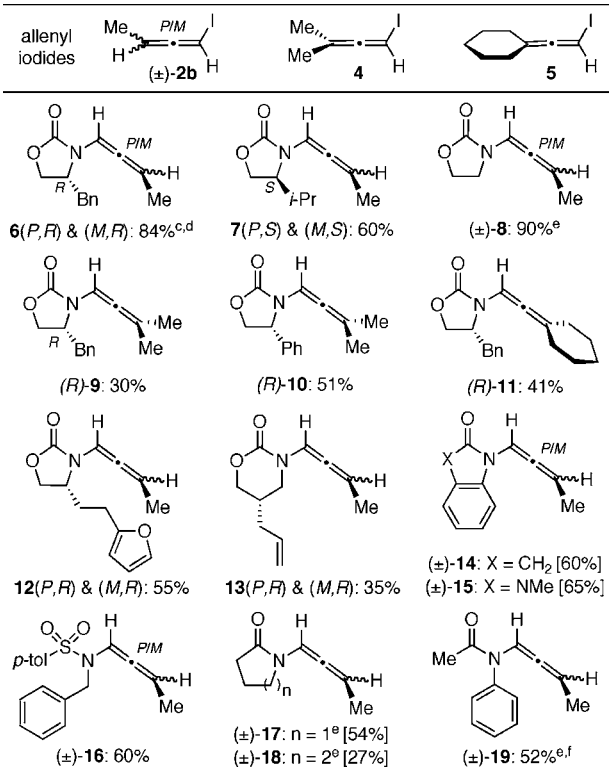


Figure 1. Generality of the amidative cross-coupling. [a]Unless otherwise indicated, all reactions were run in toluene at 50 °C using 10 mol% CuCN, 20 mol% DMEDA, and 2 equiv of Cs_2CO_3 . [b]-Isolated yields. [c]Reaction was run at rt. [d]Yield: 69% at 50 °C. [e]-Performed with 10 mol% CuTC [Cu(I) thiophenecarboxylate]. [f]Yield: 39% using CuCN.

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1−3].[19] Cu(I) salts such as CuI and CuCN and DMEDA appeared to be the best catalytic combination [entries 6, 7, 9, 11, 12], although 1,10-phenanthroline was also quite feasible [entries 4, 8, and 10].

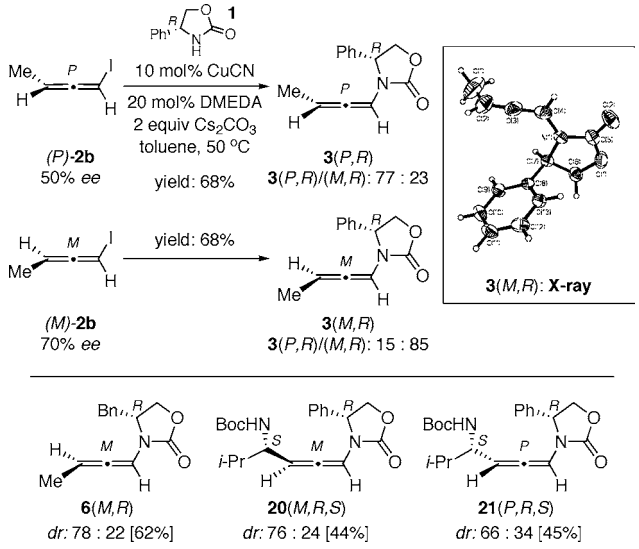
Temperature appears to be a critical factor. Despite possessing a much improved thermal stability over allenamines [or 1-amino-allenes],[20] not all allenamides are robust at temperatures well over 100 °C, and they possess variable stability at 80−90 °C. Therefore, these amidative cross-couplings were best carried out at 50 °C or room temperature.

The generality of this cross-coupling reaction using various amides and allenyl iodides can be distinctly illustrated as shown in Figure 1. The scope of amides would include chiral and achiral cyclic urethanes, cyclic urethanes containing furyl and alkenyl functional groups, 2-oxoindole, benzimidazolidinone, sulfonamide, lactams, and acyclic amides.

Allenyl iodides would include (±)-**2b** and 1-iodo-2,2-dimethyl-1,2-propadiene **4**,[21] which gave the trisubstituted allenamides **9** and **10**, respectively, and 1-iodo-2-cyclohexylidene-1,2-propadiene **5**,[21] which gave the trisubstituted allenamides **11**. In addition, CuTC [copper(I) thiophenecarboxylate], used in Trost's work,[12] appeared to be superior to or at least comparable to CuCN for specific preparations of allenamides **8** and **17**−**19**.

We then turned our attention to optically enriched chiral allenyl iodides because we were curious whether the axial stereointegrity of an allenyl halide would be preserved throughout these cross-coupling conditions. As shown in Scheme 2, coupling of optically enriched allenyl iodide (*P*)-**2b**[21] with Evans' chiral oxazolidinone **1** gave allenamide **3** in 68% yield with the diastereomeric ratio of **3**(*P*,*R*) to **3**(*M*,*R*) being 77:23. This result implies that the axial chirality of (*P*)-**2b** was retained during the amidation since the enantiomeric enrichment of (*P*)-**2b** was only 50%.

Scheme 2

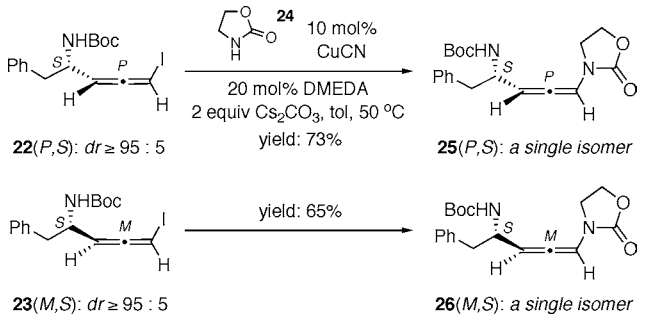


To confirm this, coupling of allenyl iodide (*M*)-**2b**[21] with an enantiomeric enrichment of 70% gave allenamide **3** in 68% yield with the **3**(*P*,*R*) to **3**(*M*,*R*) ratio being 15:85. An X-ray structure of pure **3**(*M*,*R*) was obtained to confirm the absolute configuration [Scheme 2]. This phenomenon can be observed in other couplings that gave allenamides **6**(*M*,*R*), **20**(*M*,*R*,*S*), and **21**(*P*,*R*,*S*). These reactions collectively provide solid support that the axial stereointegrity of allenyl iodide **2b** was maintained throughout the amidation process.

To demonstrate the level of stereospecificity in this amidation, we needed an optically pure allenyl iodide. However, our efforts were hampered by the fact that we could not identify any useful experimental protocols that would provide optically pure allenyl iodides such as **2b**.[20,21] Therefore, to support this stereospecific amidative cross-coupling further, we pursued the following two studies.

First, diastereomeric allenyl iodides **22** and **23** were prepared[22] and painstakingly separated using MPLC [Scheme 3]. Their couplings with achiral oxazolidinone **24**

Scheme 3



led to allenamides **25** and **26**, respectively, in 73 and 65% yield, as single diastereomers. More significantly, there was no interconversion between **25** and **26** under these conditions.

Second, as shown in Scheme 4, we employed optically enriched allenyl iodide (*P*)-**2b** [50% ee] and (*M*)-**2b** [75% and 66% ee] and found that their couplings with amides **27**

(18) See Supporting Information for experimental procedures and characterizations of new compounds.

(19) Trost reported some successful examples of couplings with allenyl bromide. See ref 12.

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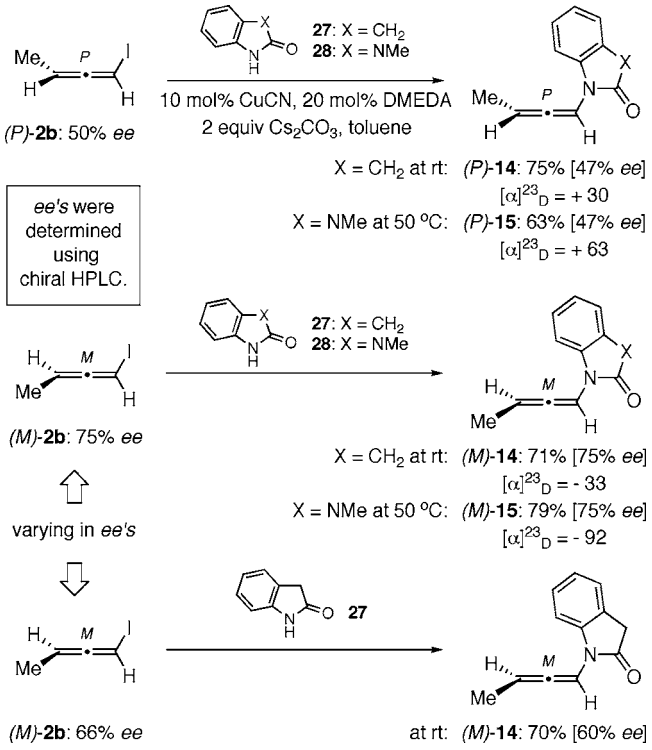
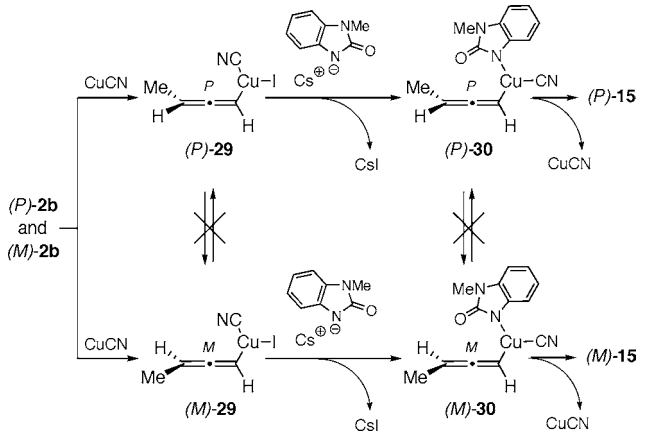
Scheme 4



and **28**[23] under standard conditions gave allenamides (*P*)-**14** and (*P*)-**15**, and (*M*)-**14** and (*M*)-**15**, respectively, with enantiomeric excesses that are closely matched with the initial optical enrichment in (*P*)-**2b** and (*M*)-**2b**. More importantly, the ee of (*M*)-**14** varied with the ee of (*M*)-**2b**. In addition, it is noteworthy that allenamides (*P*)- and (*M*)-**14**, and (*P*)- and (*M*)-**15**, represent the first examples of an optically enriched allenamide with respect to its axial chirality without any external chiral entities.

(23) These amides were chosen because we were able to resolve their respective enantiomeric allenamides distinctly on using HPLC on a Chiralcel-OD chiral column with a UV detector [see Supporting Information].

Scheme 5



On the basis of the generally accepted amidation mechanism,[1,2,3b] this evidence strongly suggests that allenyl copper(III) species (*P*)-**29** and (*M*)-**29** [Scheme 5], formed after the oxidative addition, maintain the axial stereointegrity that was inherited from the chiral allenyl iodide. This integrity would persist under the reaction conditions employed here throughout the cross-coupling process that would include transmetalation to give (*P*)-**30** and (*M*)-**30** followed by reductive elimination.

We have described here a novel stereospecific amidation of chiral allenyl iodides. This work provides an excellent synthetic entry to optically enriched allenamides.

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Supporting Information Available: Experimental procedures, NMR spectra and characterizations for all new compounds, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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