

Ligand-Controlled Regiodivergence in the Copper-Catalyzed [2,3]- and [1,2]-Rearrangements of Iodonium Ylides

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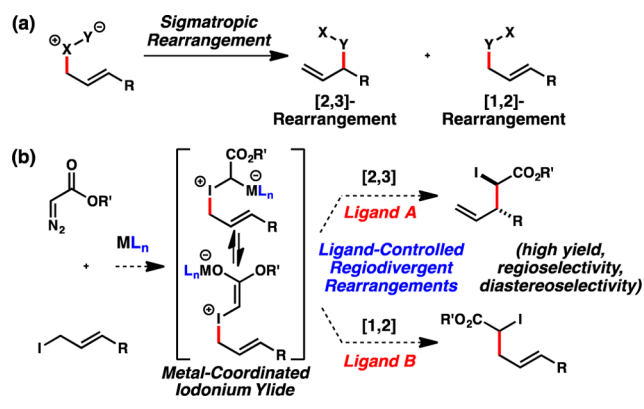
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S Supporting Information

ABSTRACT: Despite the importance of allylic ylide rearrangements for the synthesis of complex molecules, the catalyst control of [2,3]- and [1,2]-rearrangements remains an unsolved problem. We developed the first regiodivergent [2,3]- and [1,2]-rearrangements of iodonium ylides that are controlled by copper catalysts bearing different ligands. In the presence of a 2,2'-dipyridyl ligand, diazoesters and allylic iodides react via a [2,3]-rearrangement pathway. Alternatively, a phosphine ligand favors the formation of the [1,2]-rearrangement product. A series of α -iodoesters containing a broad range of functional groups were obtained in high yields, regioselectivities, and diastereoselectivities. Deuterium-labeling studies suggest distinct mechanisms for the regioselective rearrangements.

Signatropic rearrangements of ylides represent a powerful set of reactions for the synthesis of complex and valuable products.¹ Unfortunately a challenge remains, since this class of substrates can often access multiple products via divergent reaction pathways. For example, allylic ylides undergo [2,3]- or [1,2]-rearrangements depending on the steric and electronic properties of the substrate (Scheme 1a).² To the best of our

Scheme 1. Regiodivergent [2,3]- and [1,2]-Rearrangements



knowledge, there are no ligand-controlled catalytic methods for selecting one pathway over another,³ which may be attributed to the high reactivity of allylic ylides and the lack of any models for catalyst control over the divergent processes. The ability to impart a high level of control over this class of rearrangements would greatly increase their synthetic utility.

In this Communication, we describe the first example of a switch in selectivity from [2,3]-rearrangements to [1,2]-rearrangements of allylic ylides that is controlled by the ligand on the metal catalyst. We selected iodonium ylides⁴ to showcase this novel divergence in reactivity (Scheme 1b). The products of these transformations are α -iodoesters that are synthetically challenging to access with high selectivity by other known methods.

Due to the high reactivity of iodonium ylides, we hypothesized that the *in situ* generation of these substrates from allylic iodides and diazoesters would provide the ideal platform for developing regiodivergent metal-catalyzed rearrangements.⁴ This tandem ylide generation/rearrangement would obviate the need for isolating reactive iodonium ylides. Furthermore, the same metal catalyst could be utilized to generate the iodonium ylide and control the selectivity of the rearrangement. Although examples of copper- and rhodium-catalyzed iodonium ylide generation/[2,3]-rearrangement have been reported,⁴ rhodium carbenoids are thought to dissociate more readily from ylide intermediates generated from diazoesters.⁵ Therefore, copper was selected to maximize the likelihood of observing unprecedented ligand control of regioselectivity in the rearrangement step.⁶

We first optimized the copper-catalyzed [2,3]-rearrangement of iodonium ylides (Table 1). In the presence of commercially available $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ and in the absence of an external ligand, *E*-cinnamyl iodide (*E*)-1a and benzyl diazoester 2a yielded an unremarkable mixture of [2,3]- and [1,2]-rearrangement products 3 and 4 (61:39 rr), and 3 was formed in poor diastereoselectivity (entry 1). The effect of various ligands on the regioselectivity and diastereoselectivity of this process was examined (entries 2–6). [2,3]-Rearrangement product 3 was generated with low levels of selectivity in the presence of catalytic dipyrin-2-ylmethane (L1), 1,10-phenanthroline (L2), 2,2'-bipyridyl (L3), and 6,6'-dimethoxy-2,2'-dipyridyl (L4). However, a catalyst composed of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ and 6,6'-dibromo-2,2'-dipyridyl (L5) furnished the [2,3]-rearrangement product 3 in high regioselectivity (>95:5 rr), albeit in poor diastereoselectivity (48:52 dr). The use of *Z*-cinnamyl iodide (*Z*)-1a enhanced the diastereoselectivity of the process (entry 7) without affecting the regioselectivity. A screen of other copper sources identified $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ as the optimal precatalyst for the reaction (entries 7–9). An examination of temperature revealed that a higher regio-

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Table 1. Optimization of [2,3]-Rearrangement^a

Reaction scheme for [2,3]-rearrangement: allylic iodide (*E*)-1a (R¹=Ph, R²=H) or (*Z*)-1a (R¹=H, R²=Ph) reacts with benzyl diazoester 2a (R=Bn) or 2b (R=*t*-Bu) in the presence of a copper catalyst (5 mol%) and a ligand (6 mol%) in CH₂Cl₂ at temperature T to form product 3 or 4.

Ligands: L1 (1,10-phenanthroline), L2 (2,2',6,6'-tetrakis(2-pyridyl)pyrene), L3 (2,2',6,6'-tetrakis(2-pyridyl)pyrene with R=H), L4 (2,2',6,6'-tetrakis(2-pyridyl)pyrene with R=MeO), L5 (2,2',6,6'-tetrakis(2-pyridyl)pyrene with R=Br).

| entry | ligand | [Cu] | T (°C) | yield (%) | 3:4 | anti:syn (3) |
|-------------------|--------|---|--------|-----------|-------|--------------|
| 1 | none | [Cu(MeCN) ₄ PF ₆] | 25 | 13 | 61:39 | 36:64 |
| 2 | L1 | [Cu(MeCN) ₄ PF ₆] | 25 | 65 | 45:55 | 29:71 |
| 3 | L2 | [Cu(MeCN) ₄ PF ₆] | 25 | 64 | 20:80 | 25:75 |
| 4 | L3 | [Cu(MeCN) ₄ PF ₆] | 25 | 60 | 14:86 | 20:80 |
| 5 | L4 | [Cu(MeCN) ₄ PF ₆] | 25 | 64 | 62:38 | 40:60 |
| 6 | L5 | [Cu(MeCN) ₄ PF ₆] | 25 | 69 | >95:5 | 48:52 |
| 7 ^b | L5 | [Cu(MeCN) ₄ PF ₆] | 25 | 81 | >95:5 | 80:20 |
| 8 ^b | L5 | (CuOTf) ₂ · ¹ / ₂ PhMe | 25 | 53 | 89:11 | 76:24 |
| 9 ^b | L5 | CuCl | 25 | <5 | | |
| 10 ^b | L5 | [Cu(MeCN) ₄ PF ₆] | 45 | 71 | 94:6 | 80:20 |
| 11 ^b | L5 | [Cu(MeCN) ₄ PF ₆] | 0 | 85 | >95:5 | 81:19 |
| 12 ^b | L5 | [Cu(MeCN) ₄ PF ₆] | -20 | 92 | >95:5 | 81:19 |
| 13 ^{b,c} | L5 | [Cu(MeCN) ₄ PF ₆] | -20 | 91 | >95:5 | 94:6 |

^aReaction conditions: allylic iodide (*E*)-1a (0.4 mmol), benzyl diazoester 2a (1.2 equiv), copper catalyst (5 mol%), ligand (6 mol %), CH₂Cl₂ (0.1 M). ^b(*Z*)-1a was utilized. ^c*tert*-Butyl diazoester 2b was utilized.

selectivity and yield are obtained at lower temperatures (-20 °C) (entries 10–12). To increase the diastereoselectivity to a more synthetically useful level, we utilized more sterically encumbered *tert*-butyl diazoester 2b to afford [2,3]-rearrangement product in 91% yield, >95:5 rr, and 94:6 dr (entry 13).

Next, we optimized the formation of [1,2]-rearrangement product 4 by first identifying a class of ligands that favor this alternate reaction pathway (Table 2). Bidentate phosphine ligands L6–L8 and tridentate phosphine ligand L13 furnished almost exclusively [1,2]-rearrangement product 4 as a single *E*-olefin isomer (entries 1–3, 8). In the presence of monodentate trialkylphosphine ligand L12, an unfavorable mixture of regioisomers was formed (entry 7). However, monodentate triarylphosphine ligands L9–L11 facilitated the formation of [1,2]-rearrangement product 4 in >95:5 rr (entries 4–6). To emphasize the regiodivergence of these ligand-controlled rearrangements, we utilized the same *tert*-butyl diazoester 2b in the [1,2]-rearrangement that was optimal for the [2,3]-rearrangement. This bulky diazoester did not have any impact on the efficiency or selectivity of the [1,2]-rearrangement (entry 9). By performing the reaction at the elevated temperature of 45 °C in the presence of monodentate phosphine ligand L11, we observed a drastically improved

Table 2. Optimization of [1,2]-Rearrangement^a

Reaction scheme for [1,2]-rearrangement: allylic iodide (*E*)-1a (R¹=Ph, R²=H) or (*Z*)-1a (R¹=H, R²=Ph) reacts with benzyl diazoester 2a (R=Bn) or 2b (R=*t*-Bu) in the presence of a copper catalyst (5 mol%) and a ligand (6 mol%) in CH₂Cl₂ at temperature T to form product 3 or 4.

Ligands: L6 (1,1'-bis(diphenylphosphino)ethane, n=2), L7 (1,1'-bis(diphenylphosphino)ethane, n=3), L8 (1,1'-bis(diphenylphosphino)ethane, n=4), L9 (tris(diphenylphosphino)methylbenzene, R=Ph), L10 (tris(diphenylphosphino)methylbenzene, R=4-FC₆H₄), L11 (tris(diphenylphosphino)methylbenzene, R=4-MeOC₆H₄), L12 (tris(diphenylphosphino)methylbenzene, R=Cyclohexyl).

| entry | ligand | T (°C) | time (h) | yield (%) | 3:4 | Z:E (4) |
|-------------------|------------------|--------|----------|-----------|-------|---------|
| 1 | L6 | 25 | 24 | 34 | 5:>95 | 0:100 |
| 2 | L7 | 25 | 24 | 64 | 5:>95 | 0:100 |
| 3 | L8 | 25 | 24 | 56 | 5:>95 | 0:100 |
| 4 | L9 ^d | 25 | 24 | 60 | 5:>95 | 0:100 |
| 5 | L10 ^d | 25 | 24 | 56 | 5:>95 | 0:100 |
| 6 | L11 ^d | 25 | 24 | 69 | 5:>95 | 0:100 |
| 7 | L12 ^d | 25 | 36 | 18 | 70:30 | 0:100 |
| 8 | L13 | 25 | 48 | 56 | 5:>95 | 0:100 |
| 9 ^c | L11 ^d | 25 | 18 | 68 | 5:>95 | 0:100 |
| 10 ^c | L11 ^d | 45 | 6 | 92 | 0:100 | 0:100 |
| 11 ^{b,c} | L11 ^d | 45 | 6 | 91 | 5:>95 | 37:63 |

^aReaction conditions: allylic iodide (*E*)-1a (0.4 mmol), benzyl diazoester 2a (1.2 equiv), copper catalyst (5 mol%), ligand (6 mol %), CH₂Cl₂ (0.1 M). ^b(*Z*)-1a was utilized. ^c*tert*-Butyl diazoester 2b was utilized. ^d12 mol% ligand.

yield of 92% for the formation of [1,2]-rearrangement product, which was isolated in 100:0 rr (entry 10). Interestingly, when pure *Z*-cinnamyl iodide (*Z*)-1a was subjected to these optimized conditions, [1,2]-rearrangement product was isolated as a 37:63 mixture of *Z*:*E* olefin isomers (entry 11), which provides insight into the mechanism of this process (*vide infra*).

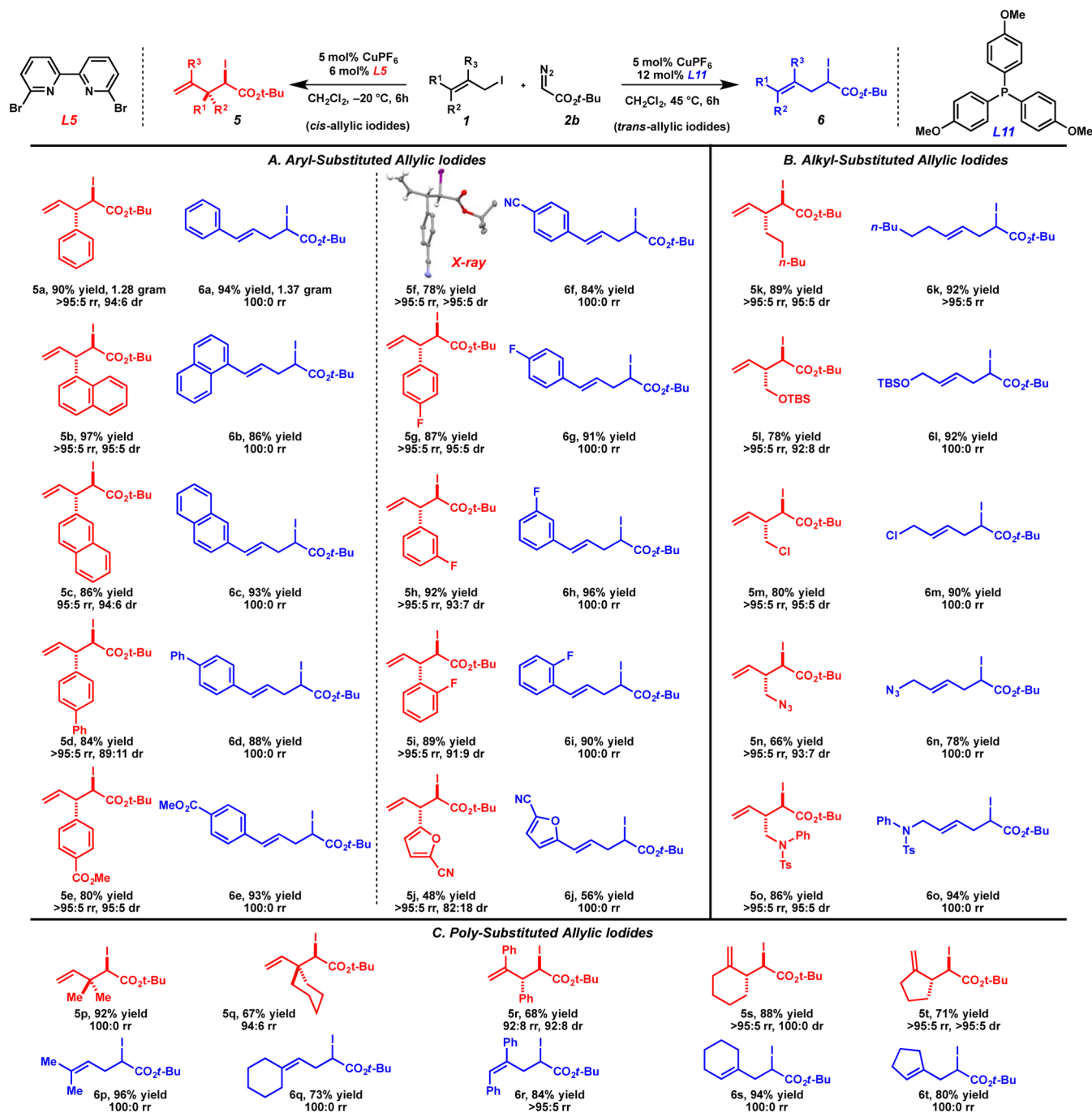
With optimized reaction conditions in hand for both the copper-catalyzed [2,3]- and [1,2]-rearrangements of iodonium ylides, we explored the functional group compatibility of these regiodivergent rearrangements (Table 3). Both reaction conditions exhibited similar tolerance to aromatic systems with a broad range of substituents (5a–5i and 6a–6i, Table 3A). Products were universally generated in good yields, high regioselectivities, and high diastereoselectivities. Substitution at the *ortho*-, *meta*-, and *para*-positions of the aromatic rings did not affect the efficiency of the reactions. Products containing heteroaromatic rings were also accessible with high regioselectivities (5j and 6j).

We expanded the scope of the [2,3]- and [1,2]-rearrangements to alkyl substituted allylic iodides (5k–5o and 6k–6o, Table 3B). Products were generated in high yields, regioselectivities, and diastereoselectivities in the presence of several functional groups, including a silyl ether, chloride, azide, and protected amine.

Notably, we subjected poly-substituted allylic iodides to the regiodivergent rearrangements, which furnished products with significantly different architectures that would be difficult to access by traditional methods (5p–5t and 6p–6t, Table 3C). These examples highlight the potential of iodonium ylide rearrangements to generate a diverse collection of products from the same set of starting materials.

Gratifyingly, the efficiency of [2,3]- and [1,2]-rearrangements was maintained on gram scale, as we formed 1.28 g of 5a (90%

Table 3. Substrate Scope of Copper-Catalyzed [2,3]- and [1,2]-Rearrangements of Iodonium Ylides



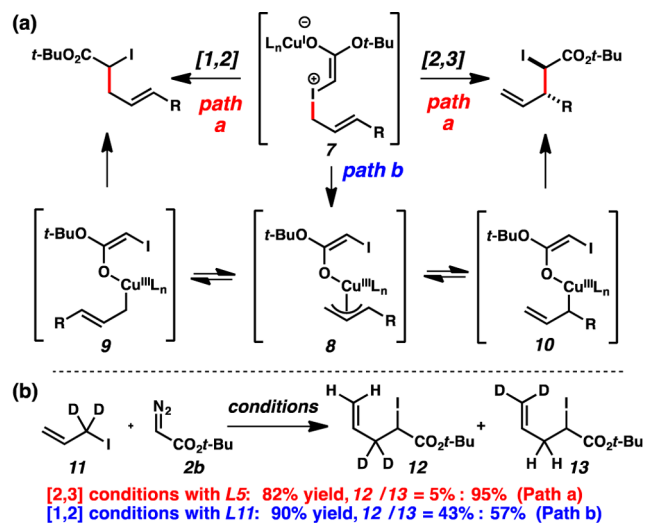
yield) and 1.37 g of **6a** (94% yield) under the optimized conditions.

We propose two possible mechanisms for the copper-catalyzed regiodivergent [2,3]- and [1,2]-rearrangements of iodonium ylides (Scheme 2a). In both scenarios, we surmise that the diazoester and allylic iodide combine to form copper-coordinated iodonium ylide **7**. This intermediate can undergo a concerted charge-induced rearrangement (path a). Alternatively, the rearrangement products can be formed through a stepwise oxidative addition/reductive elimination mechanism (path b), which proceeds through interconverting copper(III)-allyl complexes **8**, **9**, and **10**.⁷

We devised deuterium-labeled experiments to distinguish between these two possible mechanisms (Scheme 2b). Diazoester **2b** and deuterated allylic iodide **11** were subjected to both reaction conditions. Terminal allylic iodide **11** was selected to avoid any steric bias that may exist for a substituted allylic iodide. Whereas the optimized [2,3]-rearrangement conditions led to the formation of product **13** with fidelity in the transposition of deuterium, the optimized [1,2]-rearrangement conditions yielded a mixture of deuterated products **12** and **13**.

Based on these experiments, we propose that the copper-catalyzed [2,3]-rearrangement in the presence of 2,2'-bipyridyl ligand **L5** proceeds through a concerted charge-induced

Scheme 2. Mechanistic Studies



rearrangement mechanism (path a), and the copper-catalyzed [1,2]-rearrangement with monodentate phosphine ligand **L11** proceeds through a copper(III)-allyl complex that is formed via a stepwise oxidative addition/reductive elimination mechanism (path b). We hypothesize that the diminished σ -donicity of 2,2'-bipyridyl ligand **L5** decreases the reactivity of metal-coordinated iodonium ylide **7** toward oxidative addition, which favors the formation of the [2,3]-rearrangement product via the concerted charge-induced rearrangement mechanism. Alternatively, the strong σ -donating phosphine ligand **L11** facilitates oxidative addition of metal-coordinated iodonium ylide **7** to form copper(III)-allyl complexes **8-10**,⁷ which leads to the formation of the [1,2]-rearrangement product via subsequent reductive elimination.

In conclusion, we have developed regiodivergent copper-catalyzed [2,3]- and [1,2]-rearrangements of iodonium ylides. These results represent the first example of switching selectivity from [2,3]-rearrangements to [1,2]-rearrangements of allylic ylides that is controlled by the ligand of the metal catalyst. Both reactions demonstrate a broad substrate scope and functional group tolerance of aryl and aliphatic allylic iodides. Mechanistic studies are consistent with different mechanisms for the regiodivergent rearrangements. We are currently exploring enantioselective versions of these processes and their application to the synthesis of complex target molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08624.

Experimental procedures and characterization data (PDF)

X-ray crystallographic data for **1** (CIF)

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Notes

The authors declare no competing financial interest.

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