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Copper-Catalyzed Enantioselective, Diastereoselective, and Regioselective [2,3]-Rearrangements of Iodonium Ylides

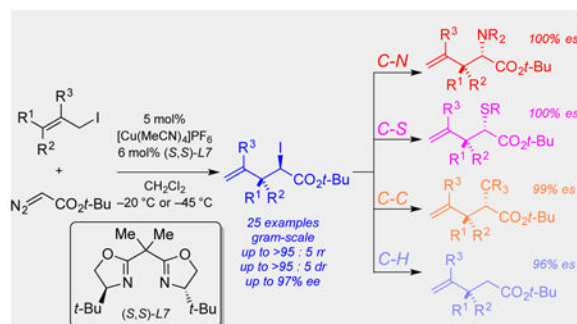
Bin Xu, Dr. and Uttam K. Tambar, Prof. Dr.*

Dedicated to Professor Qi-Lin Zhou on the occasion of his 60th birthday

Abstract

The first highly enantioselective, diastereoselective, and regioselective [2,3]-rearrangement of iodonium ylides has been developed as a general solution to catalytic onium ylide rearrangements. In the presence of a chiral copper catalyst, substituted allylic iodides couple with α -diazooesters to generate metal-coordinated iodonium ylides, which undergo [2,3]-rearrangements with high selectivities (up to >95:5 rr, up to >95:5 dr, and up to 97% ee). The enantioenriched iodoester products can be converted stereospecifically to a variety of onium ylide rearrangement products, as well as compounds that are not accessible via classical onium ylide rearrangements.

Graphical abstract



A highly enantio-, diastereo-, and regioselective [2,3]-rearrangement of iodonium ylides is reported as a general solution to catalytic onium ylide rearrangements. In the presence of a chiral copper catalyst, substituted allylic iodides couple with α -diazooesters to generate metal-coordinated iodonium ylides, which undergo [2,3]-rearrangements with high selectivities. The enantioenriched iodoester products are converted stereospecifically to a variety of useful chiral building blocks.

Keywords

iodonium; ylide; [2; 3]-rearrangement; copper; iodoester

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Catalytic enantioselective [2,3]-onium ylide rearrangements are historically important reactions that have been utilized for the synthesis of structurally complex chiral molecules.^[1,2] The power of these transformations lies in their ability to convert achiral starting materials into products with vicinal stereocenters in high enantioselectivity and diastereoselectivity. In this context, catalytic processes via metal carbenoid intermediates have been especially useful (Scheme 1A). Traditional approaches have relied on the use of different conditions for the individual development of [2,3]-rearrangements of allylic ammonium,^[3] sulfonium,^[4] and oxonium^[5] ylides.^[6] We were interested in developing a more unified approach to [2,3]-onium ylide rearrangements. We envisioned that the discovery of an enantioselective and diastereoselective [2,3]-iodonium ylide rearrangement would provide access to chiral iodoesters that could be converted stereospecifically to products of many onium ylide rearrangements. Moreover, we could access products that are not accessible via classical onium ylide rearrangements.

Despite the potential utility of iodonium ylide rearrangements as a versatile class of reactions, selective [2,3]-rearrangements of these substrates have been rarely investigated.^[7] In particular, substituted allylic iodonium ylides can generate up to 8 isomeric products via unselective [2,3]- and [1,2]-rearrangements (Scheme 1B). We recently reported the regioselective [2,3]- and [1,2]-rearrangements of iodonium ylides for the generation of racemic iodoester products.^[8] Seminal studies by Doyle and co-workers reported that a single iodonium ylide substrate generated from unsubstituted allylic iodide underwent enantioselective rearrangement (69% ee), but there was no indication of the regioselectivity or diastereoselectivity.^[9] To date, there are no catalytic rearrangements of these reactive substrates that can generate one product in high selectivity. In this Communication, we describe the first highly enantioselective, diastereoselective, and regioselective [2,3]-rearrangements of substituted iodonium ylides, and we disclose the synthetic versatility of the resulting iodoester products (Scheme 1C).

We commenced our studies with the substituted cinnamyl iodide (*E*)-**1a** and coupled it with benzyl α -diazoester **2a** in the presence of 5 mol% [Cu(MeCN)₄]PF₆ and 6 mol% of various ligands (entries 1-9). Phosphine ligands BINAP **L1**, phosphoramidite **L2**, and QUINAP **L3** favored the formation of [1,2]-rearrangement product **4** (entries 1-3).^[10] Alternatively, bisoxazoline ligands **L4-L9** preferentially yielded [2,3]-rearrangement product **3** with a range of regioselectivities, diastereoselectivities, and enantioselectivities (entries 4-9). *t*-Butyl-substituted bisoxazoline **L7** provided the best regioselectivity and enantioselectivity for the [2,3]-rearrangement (entry 7, 87:13 rr, 75% and 81% ee). A screen of alternate copper sources in the presence of optimal ligand **L7** did not improve the selectivities (entries 10-12). When cinnamyl iodide (*E*)-**1a** was replaced with its olefin isomer (*Z*)-**1a**, the diastereoselectivity (80:20) was drastically improved without affecting the regioselectivity (entry 13). To our delight, the bulkier *t*-butyl α -diazoester **2b** reacted with cinnamyl iodide (*Z*)-**1a** with enhanced enantiomeric excess (entry 14, 82% ee). A screen of temperatures (entries 14-16) revealed -20 °C as the optimal temperature for this process. Under these conditions, [2,3]-iodonium ylide rearrangement product **3** was isolated in 82% yield, >95:5 rr, >95:5 dr, and 96% ee (entry 16).

Using the optimal conditions, we evaluated the reactions of various aryl-substituted allylic iodides **1a–m** with *t*-butyl α -diazoester **2b** (Table 2). The enantioselective rearrangement exhibited good tolerance to different aromatic hydrocarbon rings (**5a–5d**). Substituents at the *para* or *meta* positions of the aryl ring had a negligible impact on the yield and selectivity of the reaction. Substrates with either electron-withdrawing groups (ketone, ester, amide, fluoro and trifluoromethyl) or with electron-donating groups (methyl and trifluoromethoxy), underwent [2,3]-rearrangement smoothly and afforded the corresponding chiral α -iodoester products (**5e–5k**) in good yields (63–87%) with excellent selectivities (up to >95:5 rr, up to >95:5 dr, and 90–97% ee). Aryl-substituted allylic iodides with *ortho* substituents (**5l–5m**) afforded very good diastereoselectivities (>95:5 dr) and enantioselectivities (95% ee) but relatively low yields and low regioselectivities. Upon transformation of iodoester **5i** to primary alcohol **6i**, rearrangement product **5i** was determined to have the (2*R*,3*S*)-configuration by means of X-ray diffraction analysis of a single crystal.^[11]

We also investigated the [2,3]-rearrangements of various alkyl-substituted allylic iodides **1n–r** and poly-substituted allylic iodides **1s–y** (Table 3). To obtain satisfactory enantioselectivities, the rearrangements of alkyl-substituted allylic iodides were carried out at a lower temperature (–45 °C). The [2,3]-rearrangement products were provided in good yields, regioselectivities (>95:5), diastereoselectivities (>93:7) and enantioselectivities (87–93% ee) in the presence of several functional groups, including a silyl ether, chloride, and protected amine. By using poly-substituted allylic iodides bearing 5–7 membered rings or heterocycles, structurally complex products (**5t–5x**) containing a quaternary carbon center adjacent to a stereocenter were obtained with good yields and selectivities.

Next, we performed several experiments to demonstrate the potential utility of highly selective [2,3]-iodonium ylide rearrangements as a general solution to catalytic asymmetric onium ylide rearrangements (Scheme 2). First, the enantioselective [2,3]-rearrangement of iodonium ylides could be easily conducted on gram-scale without significant reduction of the yield or selectivities (Scheme 2A).

Second, we explored stereospecific transformations of the C–I bond to other bonds (Scheme 2B). For example, the iodide in the rearrangement product **5a** was displaced by thiophenol to form a new C–S bond without any diminished enantioselectivity (**7a**). This product resembles the α -thioesters that are generated by sulfonium ylide rearrangements. Even for the much bulkier product **5v**, the C–I bond was transformed to a C–N bond with 100% es. The synthetically versatile chiral α -azidoester product (**8v**) successfully underwent a bioorthogonal click reaction with phenylacetylene to furnish a chiral α -triazoloester (**S11**).^[12]

Furthermore, we converted the iodonium ylide rearrangement products to compounds that are inaccessible via traditional onium ylide rearrangements. α -Iodoester **5a** was treated with sodium malononitrile, which resulted in the formation of product **9** with a new C–C bond in 99% es. Treatment of rearrangement product **5a** with Grignard reagent and aqueous workup converted the C–I bond to a C–H bond via magnesium-halogen exchange.^[13] The resulting chiral ester **10a** was obtained with high optical purity (96% es).

In conclusion, we developed a highly enantioselective, diastereoselective, and regioselective copper-catalyzed [2,3]-rearrangement of iodonium ylides with a broad substrate scope of substituted allylic iodides. The resulting chiral α -iodoester products can be converted stereospecifically to a variety of onium ylide rearrangement products, as well as compounds that are not accessible via classical onium ylide rearrangements. We believe this transformation will benefit stereoselective C–X bond constructions in complex molecular settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

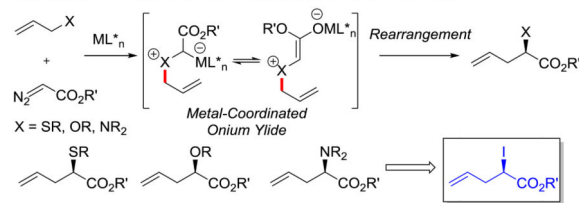
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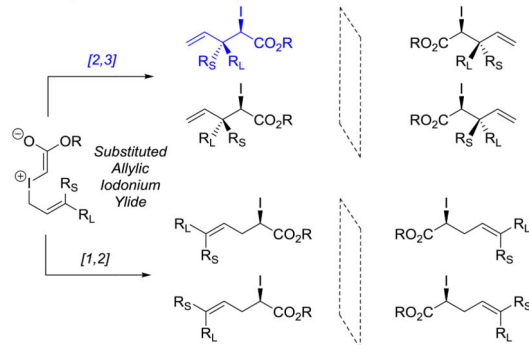
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10. The enantioselectivities for [1,2]-rearrangement product **4** were low (0% to 30% ee). For more complete optimization data, see Supporting Information.
11. See Supporting Information. CCDC 1550761 (**6i**) contains the supplementary crystallographic 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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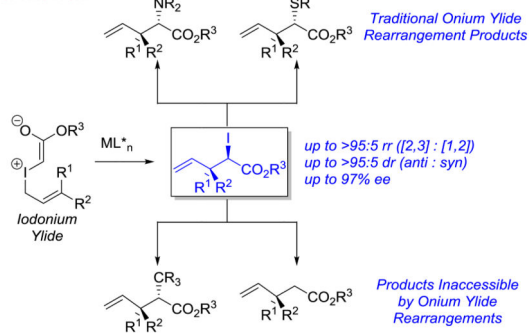
A. [2,3]-Allylic Onium Ylide Rearrangements via Metal Carbenoids



B. Challenges with Substituted Allylic Iodonium Ylides

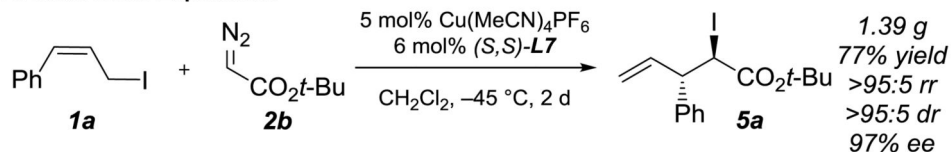


C. This Work

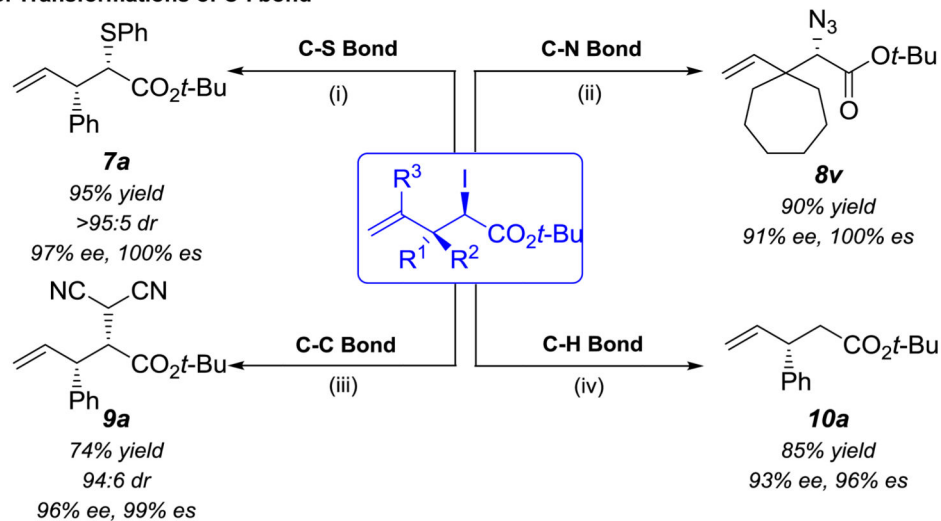


Scheme 1.
Unified Approach to Enantioselective Onium Ylide Rearrangements.

A. Gram-Scale Experiment



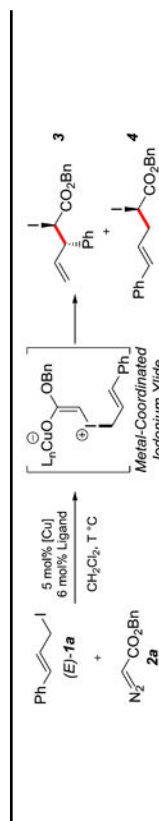
B. Transformations of C-I bond



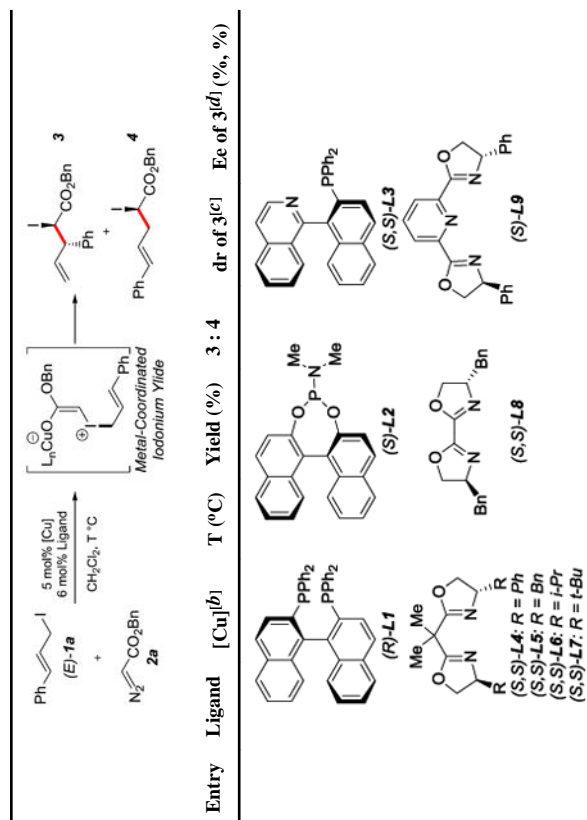
Scheme 2.

Synthetic Applications of Enantioselective [2,3]-Rearrangement Products. Regioisomeric ratio (rr) is reported as [2,3] : [1,2]. Diastereomeric ratio (dr) is reported as *anti* : *syn*. Conditions: (i) **5a** (0.1 mmol, >95:5 rr, >95:5 dr, 97% ee), 1.5 equiv PhSH, 1.5 equiv K_2CO_3 , Acetone, 23 °C, 12 h. (ii) **5v** (0.1 mmol, >95:5 rr, 91% ee), 5 equiv NaN_3 , DMSO, 90 °C, 24 h. (iii) **5a** (0.1 mmol, >95:5 rr, >95:5 dr, 97% ee), 1 equiv NaH, 1.5 equiv $CH_2(CN)_2$, THF, 80 °C, 12 h. (iv) **5a** (0.1 mmol, >95:5 rr, >95:5 dr, 97% ee), 1.1 equiv $PhCH_2CH_2MgCl$, THF, 0 °C – 23 °C, 2 h; H_2O , 23 °C.

Table 1
Optimization of Enantioselective [2,3]-Rearrangement of Iodonium Ylides^[a]



Entry	Ligand	[Cu] ^[b]	T (°C)	Yield (%)	3 : 4	dr of 3 ^[c]	Ee of 3 ^[d] (%)
1 ^[e]	(R)-L1	CuPF ₆	25	19	11 : 89	48 : 52	--
2	(S)-L2	CuPF ₆	25	21	18 : 82	58 : 42	69, 31
3	(S)-L3	CuPF ₆	25	29	<5 : 95	-- : --	--
4	(S)-L4	CuPF ₆	25	62	64 : 36	34 : 66	26, 20
5	(S)-L5	CuPF ₆	25	71	58 : 42	32 : 68	41, 31
6	(S)-L6	CuPF ₆	25	73	57 : 43	40 : 60	22, 24
7	(S)-L7	CuPF ₆	25	82	87 : 13	45 : 55	75, 81
8	(S)-L8	CuPF ₆	25	64	65 : 35	36 : 64	2, 25
9	(S)-L9	CuPF ₆	25	56	56 : 44	37 : 63	42, 12
10	(S)-L7	CuCl	25	63	60 : 40	42 : 58	10, 74
11	(S)-L7	CuOTf	25	57	74 : 26	45 : 55	56, 71
12	(S)-L7	Cu(OTf) ₂	25	59	75 : 25	45 : 55	59, 71
13 ^[f]	(S)-L7	CuPF ₆	25	80	83 : 17	80 : 20	73, 70
14 ^[g]	(S)-L7	CuPF ₆	25	85	80 : 20	91 : 9	82, --
15 ^[h]	(S)-L7	CuPF ₆	0	84	90 : 10	94 : 6	90, --
16 ^[i]	(S)-L7	CuPF ₆	-20	82	>95 : 5	>95 : 5	96, --



^[a] Reaction conditions: allylic iodide (0.4 mmol), α -diazoester (0.48 mmol), copper salt (5 mol%), ligand (6 mol%), CH_2Cl_2 (0.1M).

^[b] CuPF_6 is an abbreviation for $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$. CuOTf is an abbreviation for $(\text{CuOTf})_2 \cdot \frac{1}{2} \text{PhMe}$.

^[c] *anti* : *syn* ratio.

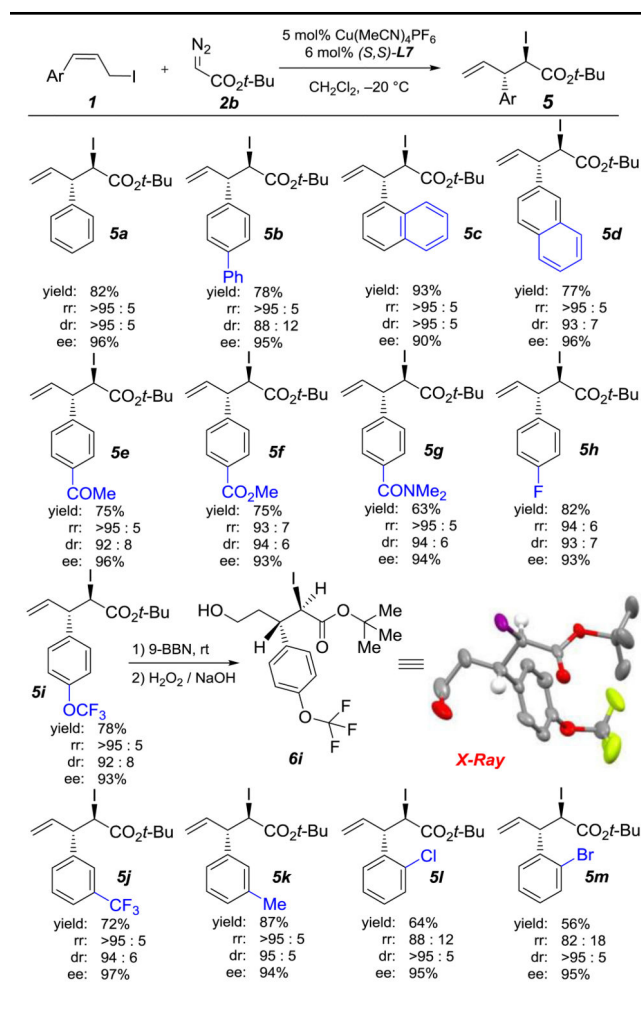
^[d] ee of *anti* diastereomer of **3**, ee of *syn* diastereomer of **3**.

^[e] 12 mol% ligand.

^[f] (*Z*)-**1a** was utilized.

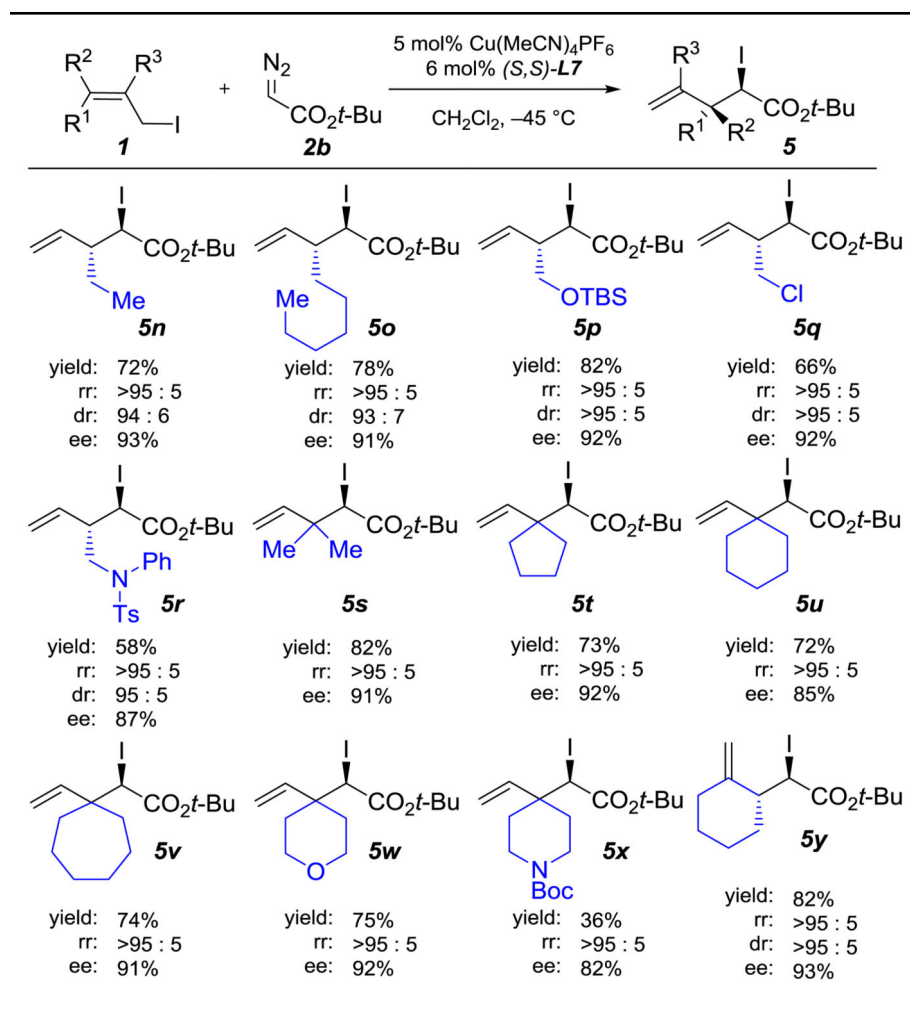
^[g] *t*-Butyldiazoester **2b** was utilized.

Table 2
Scope of Aryl-Substituted Allylic Iodides^[a]



^[a] Regioisomeric ratio (rr) is reported as [2,3] : [1,2]. Diastereomeric ratio (dr) is reported as *anti* : *syn*.

Table 3
Scope of Alkyl and Poly-Substituted Allylic Iodides^[a]



^[a] Regioisomeric ratio (rr) is reported as [2,3] : [1,2]. Diastereomeric ratio (dr) is reported as *anti* : *syn*.