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Communication

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Asymmetric Iodonio-[3,3]-Sigmatropic Rearrangement to Access Chiral α-Aryl Carbonyl Compounds

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Supporting Information Placeholder

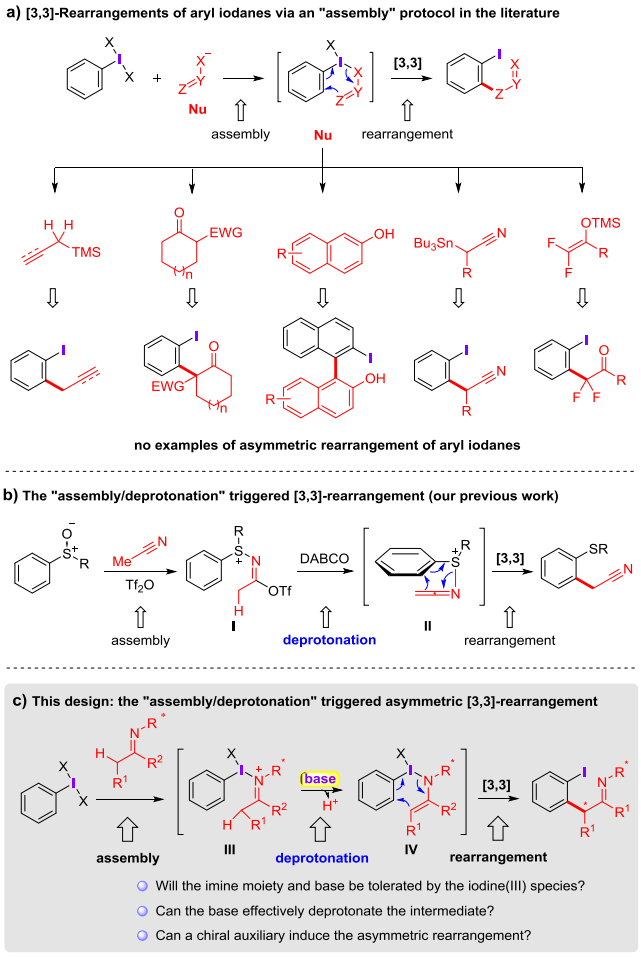
ABSTRACT: Here we describe an asymmetric [3,3]-sigmatropic rearrangement of aryl iodanes that enables the enantioselective α-arylation of chiral 2-oxazolines, thereby producing valuable, chiral α-aryl carbonyl compounds. The success of this protocol hinges on the selective assembly of aryl iodanes with 2-oxazolines and the smooth deprotonation of the in situ generated iodonium-imine species. The nearly neutral and mild conditions of the reaction allow it to tolerate a wide variety of functional groups. Moreover, the remaining iodide atom in the products not only provides a versatile platform for further elaboration of such molecules but also supplies the asymmetric hypervalent iodine chemistry with a new class of chiral scaffolds.

α-Aryl carbonyl compounds are found in a wide range of drugs and bioactive molecules.[1] Although the great advances made to synthesize these compounds,[2] the methods for accessing enantiopure α-aryl carbonyls,[3] particularly those bearing chiral tertiary benzylic centers, are rather limited.[4] This is presumably due to the relatively facile racemization of the enolizable benzylic α-carbonyl stereocenters at elevated temperatures or under basic conditions. Therefore, chiral α-aryl carbonyl compounds with tertiary C-H protons are still a particularly challenging target for synthetic chemistry.

The *ortho*-C-H functionalization of aryl iodanes with certain nucleophiles[5] has been greatly advanced since Oh's accidental discovery of *ortho*-C-H allylation of aryl iodanes with allyl silane in 1988 (Scheme 1a).[6] Until now, a wide range of nucleophiles including propargyl silanes,[7] carbonyl compounds,[8] naphthols,[9] α-stannyl nitriles,[10] and difluoroenol silyl ethers[11] have been found to be suitable for this transformation. Despite the progress made, the success of the reaction still relies heavily on the choice of a proper nucleophile that can trap electrophilic aryl iodane to assemble a subtle intermediate, which could undergo [3,3]-rearrangement to afford the final product. As a consequence, the scope of carbonyl nucleophiles is limited to structurally defined β-dicarbonyl compounds[8], toxic organotin reagents[10], and specific enol silyl ethers[11]. Not surprisingly, there have been no examples of asymmetric versions on the basis of the "assembly/rearrangement" reaction model. Therefore, new reaction patterns are required to address the severe substrate limitations and to develop the asymmetric variants.

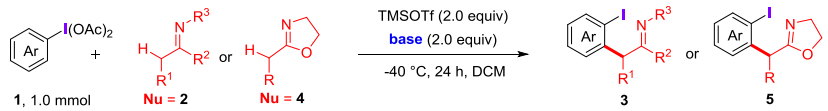
Recently, we reported an "assembly/deprotonation" protocol for developing the [3,3]-rearrangement of aryl sulfoxides with alkyl nitriles (Scheme 1b).[12a,13] The reaction proceeds via the

Scheme 1. Background and hypothesis.



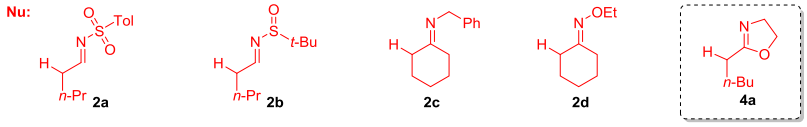
assembly of aryl sulfoxides with alkyl nitriles and deprotonation of the in situ generated imine sulfonium intermediate **I**. The independent control of each step enables the successful manipulation of unstable species **I**. As a consequence, the protocol not only addresses the substrate limitations existing in related reactions but also allows us to develop a [5,5]-rearrangement of aryl sulfoxides with allyl nitriles.[12b] Inspired by these progress (Scheme 1a and 1b)[5,12], we were interested in whether the established "assembly/deprotonation" protocol could be utilized for promoting the

Scheme 2. Development of the reaction and the substrate scope of α-arylation of 2-oxazolines 4.[a]

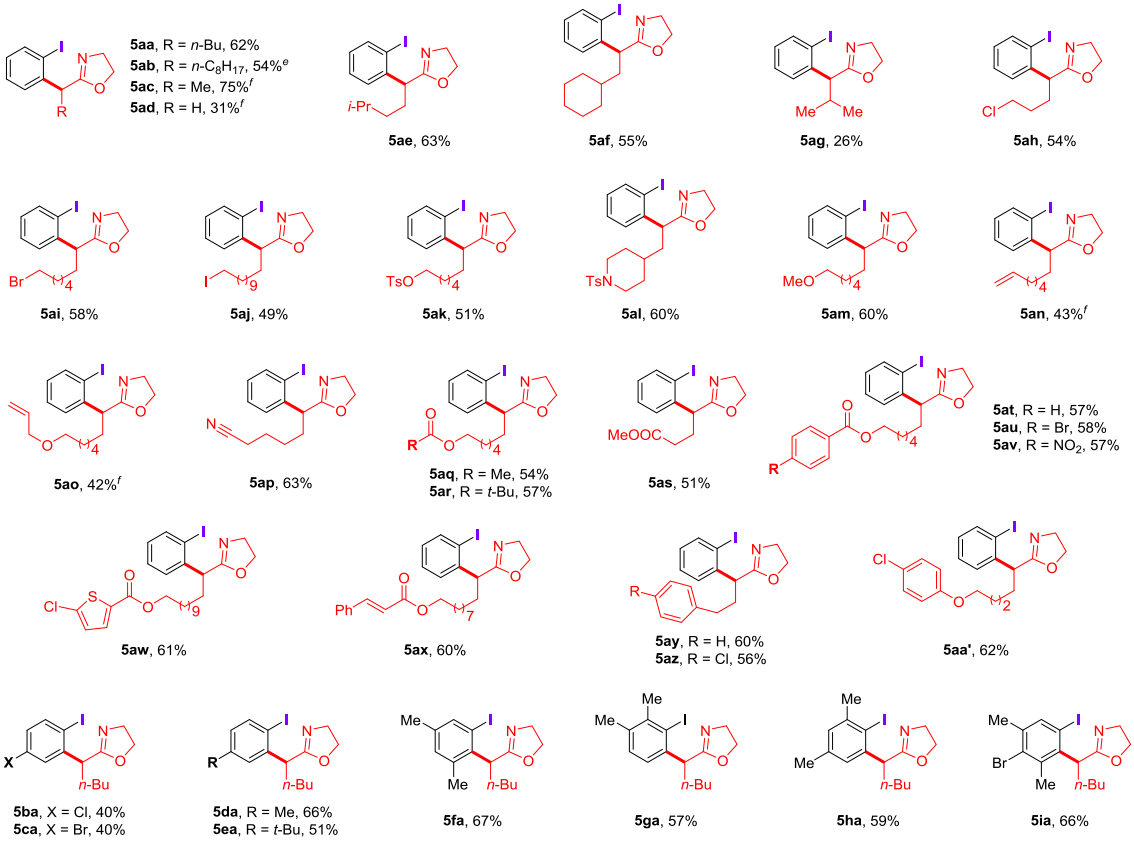


Reaction development[b]

entry	Nu	base	product/yield	entry	Nu	base	product/yield
1	**2a**	DABCO	**3aa**, 0%[c]	6	**4a**	DBU	**5aa**, 40%
2	**2b**	DABCO	**3ab**, 0%[c]	7	**4a**	*i*-Pr_2NEt	**5aa**, 9%
3	**2c**	DABCO	**3ac**, 0%[c]	8	**4a**	pyridine	**5aa**, 37%
4	**2d**	DABCO	**3ad**, 0%[c]	9	**4a**	2-methylpyridine	**5aa**, 62%
5	**4a**	DABCO	**5aa**, 28%[c]	10	**4a**	none	**5aa**, 0%



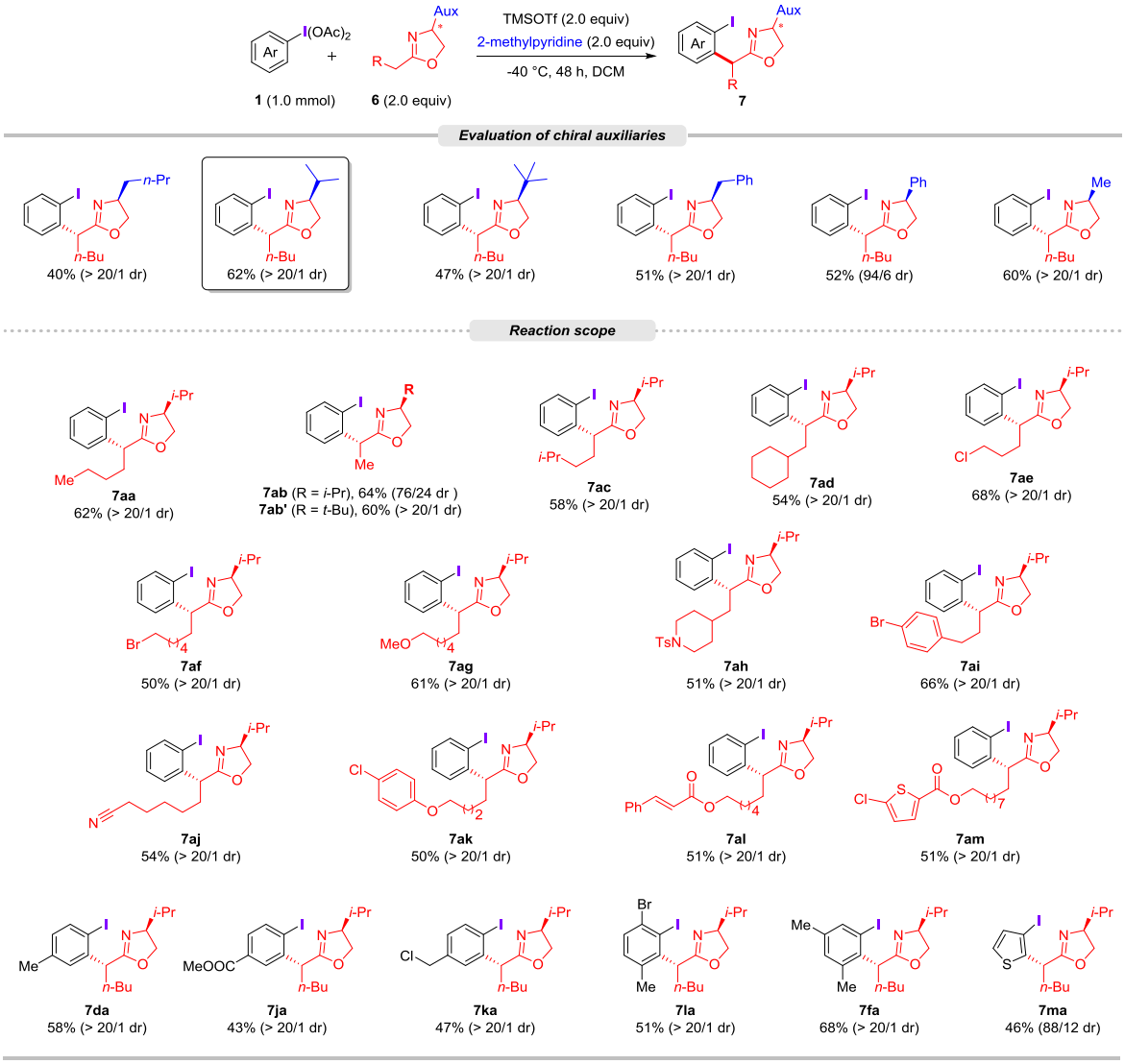
Reaction scope[d]



[a]General conditions: **1** (1.0 mmol), TMSOTf (2.0 equiv), **2** or **4** (2.0 equiv), base (2.0 equiv), DCM (0.1 M), -40 ℃ for 24 h. And isolated yields were given. [b]$PhI(OAc)_2$ **1a** was used for the reaction development. [c]The reactions were performed at -40 to rt ℃ for 24 h. PhI was obtained in approx. 13%, 34%, 66%, 56%, and 11% yields from the reactions of **2a**, **2b**, **2c**, **2d**, and **4a** respectively and 65% of **2b** and 41% of **2d** were recovered. [d]2-Oxazolines **4** were used as nucleophile and 2-methylpyridine was used as base. [e]PhI was obtained in approx. 20% yield and 59% of 2-oxazoline **4b** was recovered. [f]-40 to 0 ℃ for 12 h.

chemistry of aryl iodine(III)-mediated [3,3]-rearrangement. As illustrated in Scheme 1c, an imine moiety would serve as carbonyl analogue for trapping the electrophilic aryl iodane to assemble an iodonium-imine species **III**. This intermediate can be deprotonated by an external base to give an iodonium-enamine intermediate **IV** which would undergo [3,3]-rearrangement to afford the α-arylated imine. Furthermore, the introduction of chiral auxiliary into the imine would exert a stereochemical influence on the C-C bond forming step (rearrangement), thus achieving the stereoselective α-arylation of the chiral imine. Here, we report our development of the first asymmetric [3,3]-sigmatropic rearrangement of aryl iodanes that allows for the facile synthesis of chiral α-aryl

Scheme 3. Development of the reaction and the substrate scope of α-arylation of 2-oxazolines 4.[a,b]



[a]Reaction conditions: aryl iodane **1** (1.0 mmol), TMSOTf (2.0 equiv), chiral 2-oxazoline (2.0 equiv), 2-methylpyridine (2.0 equiv), DCM (0.1 M), -40 ℃ for 48 h. [b]Diastereomeric ratios were determined by ^{1}H-NMR analysis of the crude reaction mixtures.

carbonyl compounds. It should be noted that Maulide and coworkers recently applied the [3,3]-rearrangement protocol via a nucleophilic addition of chiral aryl sulfoxides to keteniminium species for the synthesis of chiral α-arylated amides, in which chiral sulfoxides served as the source of asymmetry.[14]

To test our hypothesis (Scheme 2), we first studied the reaction of PhI(OTf)$_2$ (formed from PhI(OAc)$_2$ **1a** and TMSOTf)[15] with different aldimines (**2a** and **2b**) and ketimines (**2c** and **2d**) (entries 1-4). DABCO previously used in the related sulfur chemistry,[12] was employed here as base. Unfortunately, in lieu of desired products **3aa-3ad**, merely PhI and imines (**2b** and **2d**) could be determined from these reactions. Excitingly, 2-oxazoline **4a** appeared to be a suitable coupling partner for the proposed reaction as it afforded the expected α-arylated oxazoline **5aa**, albeit in a relatively low yield (28%) (entry 5).[16] 2-Methylpyridine was found to be superior to other tested bases (entries 5-9) and gave the best yield of **5aa** (entry 9). Consistent with our hypothesis (Scheme 1c), the reaction indeed requires a base, since no desired product **5aa** was detected in the absence of a base (entry 10).

The substrate scope of the reaction was demonstrated in Scheme 2, below the dashed line. Regardless of the length of alkyl chain at the α-position, 2-oxazolines **4a-c** and **4e** afforded the desired products **5aa-ac** and **5ae** in modest to good yields (54-75%). It is necessary to note that in the case of **4b**, aside from desired product **5ab**, PhI was obtained in approx. 20% yield with a recovery of 59% of 2-oxazoline **4b**. The formation of PhI could be attributed to the undesired oxidations of 2-oxazoline **4b** by aryl iodine (III) species. Since no other side products were determined, the reason for the side reactions remains unclear. Impressively, **4g** bearing a bulky *i*-Pr group still afforded the desired **5ag** albeit with a poor yield (26%). Remarkably, the reaction exhibited excellent functional group (FG) compatibility. FGs including alkyl/aryl halides, Ts-protected amine, ethers, alkenes, nitriles, esters, and heteroarenes were all well tolerated in the reaction. As depicted at last raw, aryl iodanes bearing electron-donating groups (**5da-5ia**) were better suited to the reaction than those bearing electron-withdrawing groups (**5ba** and **5ca**). Surprisingly, bulkier aryl iodanes with an *ortho*-methyl group could also react with 2-oxazline **4a**, yielding desired α-aryl 2-oxazolines **5fa-5ia** in synthetically useful yields.

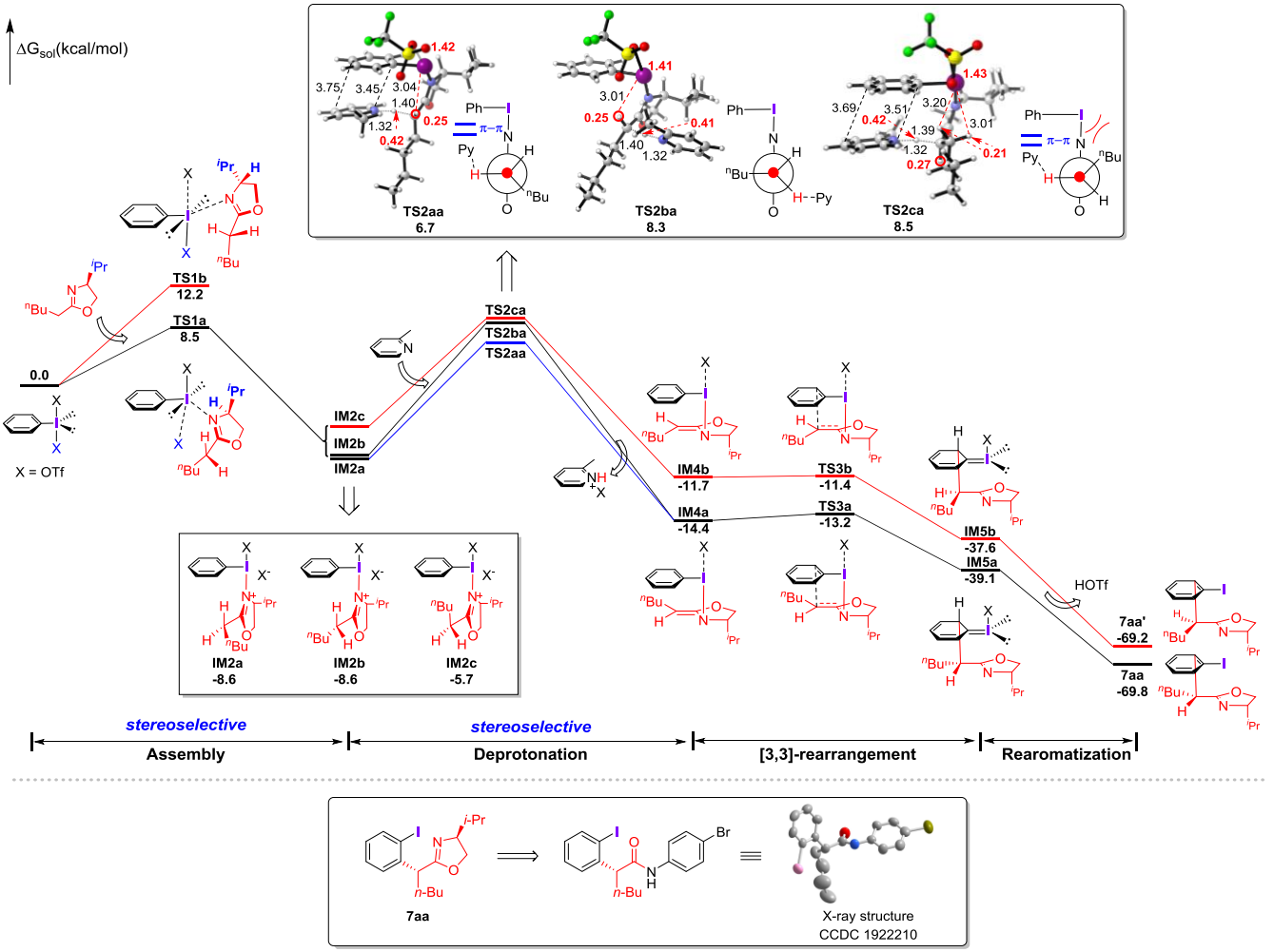
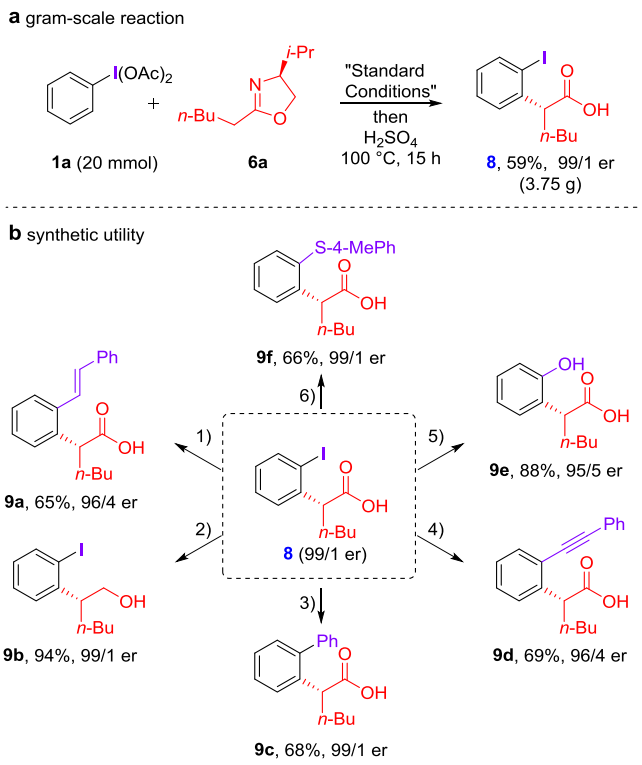


Figure 1: Simplified free energy profile for the conversion of **6a** to **7aa**/**7aa'**. Values in black and red in the optimized structures are key bond lengths in angstroms and NBO charges in *e*, respectively. X-ray structure of an amide derivative of **7aa** is given above.

Next, we examined the feasibility of an asymmetric variant of this process by using chiral 2-oxazoline as substrate (Scheme 3). To our surprise, an array of chiral 2-oxazolines proved to be suitable for the transformation giving modest to good yields with excellent diastereoselectivities (> 20/1 dr), except for the Ph-substituted chiral 2-oxazoline (94/6 dr). Remarkably, chiral 2-oxazoline with even a relatively small methyl group could achieve a very high level of diastereoselectivity (> 20/1 dr). Eventually, the *i*-Pr-substituted 2-oxazoline was identified as the most effective chiral auxiliary by giving the best yield (62%). To our delight, similar to its non-asymmetric version, the asymmetric protocol possessed a broad substrate scope for both coupling partners (Scheme 3, below the dashed line). Impressively, the reaction generally gave the desired products with excellent diastereoselectivities. Although **6b** bearing a small α-methyl group resulted in relatively low diastereoselectivity (**7ab**, 76/24 dr), switching to a bulkier substituent (*t*-Bu group) significantly improved the diastereoselectivity (**7ab'**, > 20/1 dr). In addition to arenes, heteroarene **1m** is also suitable for the reaction, albeit yielding the desired product **7ma** in a modest yield (46%) and a relatively low dr (88/12).

The configuration of the α-carbon center in the products was deuced by single-crystal X-ray analysis of a corresponding amide prepared via hydrolysis and amidation of **7aa** (Figure 1 below the dashed line). To gain deeper insight into the reaction mechanism and diastereoselectivity of our synthetic strategy, we carried out DFT computations with the conversion of **6a** to **7aa**/**7aa'** as a representative (see SI7 for computational details). Figure 1 shows the simplified version of the complete free energy profile of the reaction (see Figure S1 in SI7). The reaction proceeds via sequential four stages. The first stage assembles $PhI(OTf)_2$ and **6a** together by substitution via **TS1a**/**TS1b**. The less favorable **TS1b** than **TS1a** could be attributed to the steric congestion of auxiliary ^{i}Pr group with $PhI(OTf)_2$. Thus, the auxiliary group controls the preferential surface of oxazoline for the attack of $PhI(OTf)_2$. Due to the 3.7 kcal/mol higher **TS1b** than **TS1a**, the pathway through **TS1b** could be excluded. The first stage results in an intermediate that has three configurations (i.e. **IM2a**-**IM2c**), among which the one with ^{n}Bu *cis* to oxazoline nitrogen is least stable. The second stage undergoes deprotonation. For each of the three configurations, considering the two possible hydrogen atoms that could be removed and the two possible orientations of 2-methylpyridine methyl group with respect to ^{n}Bu group, we located four transition states for each configuration. The transition states (**TS2aa**, **TS2ba**, and **TS2ca**) represent the lowest one for each of the three cases. Examining the structures of the transition states, **TS2aa** featuring π-π interaction between pyridine and $PhI(OTf)_2$ phenyl group is most favorable. Compared to **TS2aa**, the less stable **TS2ba** can be ascribed to the absence of the π-π interaction. Despite the similar π-π interaction in **TS2ca**, it suffers two destabilizing effects, including one more repulsive I(q=1.43*e*) ··H(q=0.21*e*) Coulomb interaction and the steric effect due to the *cis* arrangement of ^{n}Bu group relative to oxazoline nitrogen, thus offsetting the favorable π-π interaction. Because the deprotonation converts the C-C

Scheme 4. Gram-scale reaction (a) and applications (b,c).



(1) $Pd(OAc)_2$ (12 mol%), P(*o*-tol)$_3$ (4 mol%), styrene, Et_3N. (2) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF. (3) $Pd(PPh_3)_4$ (10 mol%), K_3PO_4, $PhB(OH)_2$, H_2O/dioxane. (4) $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), phenylacetylene, Et_3N. (5) CuI (10 mol%), 1,10-phenanthroline (20 mol%), KOH, DMSO/H_2O. (6) CuI (20 mol%), 4-methylbenzenethiol, K_2CO_3, ethylene glycol, *tert*-amyl alcohol.

single bond to double bond, both **TS2aa** and **TS2ba** lead to the same intermediate **IM4a** with inward ^{n}Bu, while **TS2ca** gives **IM4b** with outward ^{n}Bu. The *cis* and *trans* alkenes in **IM4a** and **IM4b** determines the diastereoselectivity of the products, **IM4a** leading to **7aa** whereas **IM4b** to **7aa'** via subsequent [3,3]-sigmatropic rearrangement (the third stage) and rearomatization (the fourth stage). Energetically, the deprotonation is both rate- and selectivity-determining stage. The low rate-determining barrier (15.3 kcal/mol, **TS2aa** relative to **IM2a**) and the great exergonicity (ca. 70.0 kcal/mol) rationalize why the reaction could take place at relatively low temperature (-40 ℃). The barrier difference (1.8 kcal/mol) between **TS2aa** and **TS2ca** predicts a ratio (49:1) of **7aa**:**7aa'**, in reasonable agreement with the observed ratio of 20:1.

To demonstrate the practicality of the protocol, a gram-scale reaction followed by hydrolysis of the in situ-generated product was performed, and the process afforded the corresponding chiral α-aryl carboxlylic acid **8** in 59% yield (3.75 g) with an excellent er (99/1) (Scheme 4a). Furthermore, the utility of the method was exemplified by the elaboration of product **8** (Scheme 4b). The remaining iodide atom could be converted to other functionalities including vinyl, phenyl, alkynyl, hydroxyl and sulfide groups (**9a** and **9c**-**9f**) with the retention of stereochemistry. The carboxylic group can be reduced to an alcohol (**9b**) with a very good yield (94%) and an excellent er (99/1). The utility of the method was further demonstrated by using the enantiopure chiral aryl iodide **8** as catalyst for an asymmetric catalytic α-oxidation reaction (Scheme 4c). Although the yield was relatively low and the enantioselectivity relatively poor (34%, 62/38 er), this preliminary result indicates that the current method could be useful for asymmetric hypervalent iodine chemistry by providing a new type of chiral reagent or catalyst.

In summary, we have developed the first asymmetric iodonio-[3,3]-sigmatropic rearrangement using an "assembly/deprotonation" protocol that provides a new access to chiral α-aryl carbonyl compounds. Three features of this reaction deserve to be highlighted: (1) The use of readily available substrates including aryl iodanes and chiral 2-oxazolines highlights the practicality of the method; (2) The reaction tolerates a wide array of FGs, some of which can be challenging for other known methods; and (3) The remaining iodide atom serving as an ideal leaving group enables the diverse elaboration of the generated products into value-added synthetic targets. DFT calculations disclose that the diastereoselectivity originate from the auxiliary group which controls the preferential surface of 2-oxazoline for assembly and the π-π interaction between pyridine and $PhI(OTf)_2$ phenyl group which determines the configuration of the resulting alkene intermediate. In a word, we demonstrate the possibility of using 2-oxazolines as a three-atom unit for constructing [3,3]-rearrangement precursors with an electrophilic aryl iodine (III) species, and particularly the use of chiral auxiliary for inducing asymmetric rearrangement.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterization data, and NMR spectra for all new compounds. Materials related to DFT calculations.

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Notes

The authors declare no competing financial interests.

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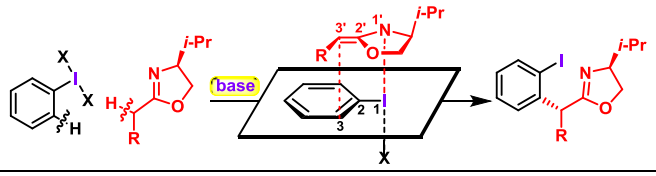
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