JOC The Journal of Organic Chemistry

Article

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A One-Pot/Single-Analysis Approach to Substrate Scope Investigations Using Comprehensive Two-Dimensional Gas Chromatography (GC×GC)

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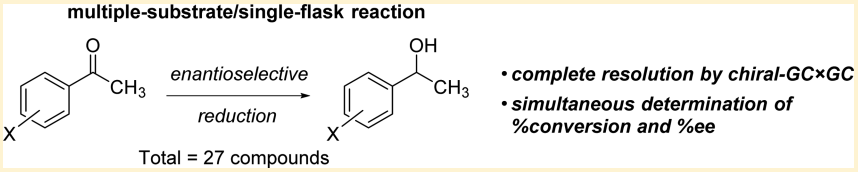
Supporting Information



ABSTRACT: A representative substrate scope investigation for an enantioselective catalytic ketone-reduction has been performed as a single reaction on a mixture containing equimolar amounts of nine (9) prototypical compounds. The resulting analyte pool containing 18 potential products from nine different reactions could all be completely resolved in a single chromatographic injection using comprehensive two-dimensional gas chromatography (GC×GC) with time-of-flight mass spectrometry, allowing for simultaneous determination of percent conversion and enantiomeric excess for each substrate. The results obtained for an enantioselective iron-catalyzed asymmetric transfer hydrogenation using this one-pot/single-analysis approach were similar to those reported for the individualized reactions, demonstrating the utility of this strategy for streamlining substrate scope investigations. Moreover, for this particular catalyst, activity and selectivity were not greatly affected by the presence of other ketones or enantioenriched reduced products. This approach allows for faster and greener analyses that are central to new reaction development, as well as an opportunity to gain further insights into other established transformations.

INTRODUCTION

Reaction development is critical within the synthetic organic community and continues to be a vibrant area of research. This encompasses not only the invention of new reactions (e.g., recent advances in the activation of "non-reactive" C−H bonds[1]), but also the optimization of "classic" transformations as the field strives toward a more "ideal synthesis".[2] Examples of the latter include studies directed toward the use of cheaper, greener, and more robust reagents along with improvements in reaction rate and selectivity. For each, it is necessary to investigate and report the substrate scope for that particular reaction. This vital information aids in elucidating mechanisms and allows others to anticipate if the reaction will be successful for their application, as well as perhaps identifies certain limitations that often drive the next round of research toward a more widely applicable method.

The scope and limitations of a reaction are often tabulated showing the structure of the different substrates tested, percent conversion (%conversion) or yield, and other values associated with selectivity if appropriate (e.g., enantiomeric excess (ee) or cis:trans ratios). While the number of substrates included in these tables varies (often dictated by compound availability), in general more is better to demonstrate the rigors with which the reaction has been tested. There is typically also some rationale as to why a particular compound is included, for instance to compare aryl vs alkyl substrates or explore potential electronic and/or steric effects.

Substrate scope investigations therefore represent a significant proportion of the total work conducted for a study of this type. A few examples of recently published methods development reports containing scope analyses with differentially substituted aromatic substrates are presented in Table 1 (where X, Y, and Z groups can be at the ortho-, meta-, and para-positions, respectively).[3−6] Considering that each compound included within these series of experiments represents an individual reaction that was performed and analyzed separately, the sheer volume of work required to complete one of these studies can be enormous. Taking this into account, Wang and Yamamoto's fairly comprehensive investigations into the scope of a nickel-catalyzed regio- and enantioselective epoxide aminolysis, which included results from more than 80 individual reactions that were separately executed and analyzed, is particularly noteworthy (select examples shown in entry 3, Table 1).[5]

Any strategy that streamlines substrate scope investigations therefore has a significant impact on the field. For instance, imagine these studies performed as a single reaction on a mixture containing all of the substrates of interest. Aside from greatly

Received: January 8, 2016
Published: April 14, 2016

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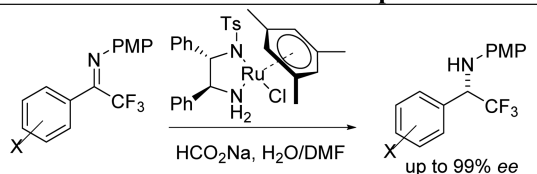
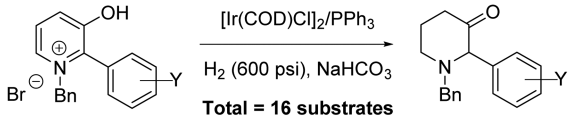
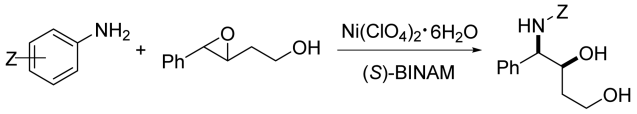
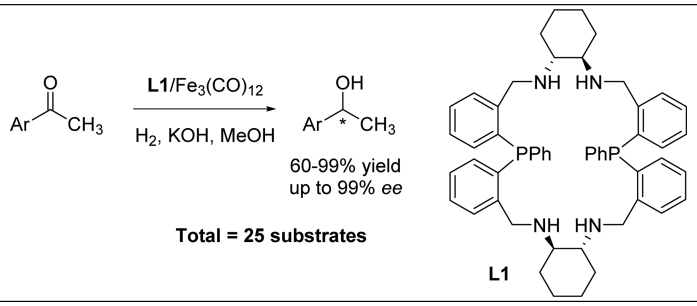
DOI: 10.1021/acs.joc.6b00050
J. Org. Chem. 2016, 81, 3533−3541

Table 1. Examples of Recent Substrate Scope Investigations Involving Differentially Substituted Aromatic Compounds Illustrating the Magnitude of Effort That Routinely Goes into Completing Studies of This Type[a]

Entry	Reference	Reaction/Substrate Scope[b]
1.	Table 3; Wu et al. *J. Org. Chem.* **2015**, *80*, 3708.	 e.g. X = F, Cl, Br, CF_3, Me **Total = 17 substrates**
2.	Figure 2; Huang et al. *Org. Lett.* **2015**, *17*, 1640	 e.g. Y = Me, OMe, F, Cl, CF_3, CO_2Me **Total = 16 substrates** 83-96% yield
3.	Schemes 2-4; Wang and Yamamoto *J. Am. Chem. Soc.* **2015**, *137*, 4308.[c]	 e.g. Z = H, OMe, Br, F, Ph, naphthyl **Total = 33 substrates** 70 - 98% yield, up to 94% *ee*
4.	Table 2; Li et al. *J. Am. Chem. Soc.* **2014**, *136*, 4031.	 60-99% yield up to 99% *ee* **Total = 25 substrates**

[a]The total number of substrates indicated is equal to the number of reactions and analyses performed. [b]Reproduced from ref 3. Copyright 2015 American Chemical Society (entry 1). Reproduced from ref 4. Copyright 2015 American Chemical Society (entry 2). Reproduced from ref 5. Copyright 2015 American Chemical Society (entry 3). Reproduced from ref 6. Copyright 2014 American Chemical Society (entry 4). [c]Scheme represents only select examples from Schemes 2−4 in the report.

reducing time and resources, this would also eliminate the possibility of any slight differences between individual reactions that might skew the results. Of course the challenge with this ideal situation becomes one of analysis. If this is part of the development of an enantioselective reaction, the analysis would involve separation of enantiomers, which due to their essentially identical physical (e.g., boiling point) and chemical (e.g., polarity) properties is nontrivial. Moreover, the proposed scenario would include multiple sets of enantiomeric pairs, some with presumably very similar structures (e.g., ortho-, meta-, and para-substituted aromatics), so that even if the enantiomers themselves could be resolved, overlap with other components (e.g., starting materials and other byproducts) might still occur. It therefore becomes clear that traditional chromatographic methods such as one-dimensional liquid chromatography or gas chromatography (GC) with chiral stationary-phases would likely not have the resolving power to monitor multiple simultaneous reactions.[7] As an example, when attempting a one-pot multisubstrate screening of the CBS-reduction, Gao and Kagan reported that it was necessary to fractionate the product mixture by flash column chromatography on silica before analysis by chiral HPLC to improve resolution.[8]

Others have commented that for many reaction screening studies, it is often the chromatographic methods that are the bottleneck.[9] As a result, there has been an interest in the development of new high-throughput techniques.[10−12] One example is multiplexing,[13] whereby many samples are (repeatedly) injected onto a separation column at short time-intervals leading to overlapping time-shifted chromatograms that can later be deconvoluted to shorten overall analysis time. Another is so-called on-column reaction gas chromatography (ocRGC),[14] using a catalytically active separation phase to essentially integrate both the reaction and analysis. With multiplexing, however, repetitive injections are necessary to unambiguously identify the individual samples,[13] and results from ocRGC are not always representative of what would be obtained from a conventional preparative-scale reaction. For instance, Fuessel and Trapp observed selectivities up to 23% ee by ocRGC for the enantioselective vanadium(IV)−salen catalyzed sulfoxidation of benzylphenylsulfide compared to only 11% ee from the conventional reaction.[15] Very recently, Bentley et al. reported a high-throughput chemosensing-based method for determination of yield and ee from Sharpless asymmetric dihydroxylation (SADH) reactions.[16] The diol product from these reactions ligates a metal complex bearing an optical chemosensor with chirality information relayed through its CD spectrum. Results from multiple runs are averaged and the ee values obtained were close (ee within 2−3%)

DOI: 10.1021/acs.joc.6b00050
J. Org. Chem. 2016, 81, 3533−3541

to the actual sample composition. This chemosensing technique, however, is still performed one-substrate at a time, with "high-throughput" referring to a more rapid analysis (15 min to analyze four (4) SADH reaction mixtures).[16]

In this paper, we describe the use of comprehensive two-dimensional gas chromatography (GC×GC) to reduce the substrate scope investigation for an enantioselective catalytic reduction to a single reaction and analysis by single injection onto a chromatographic column. GC×GC is one of the most powerful analytical tools available for the analysis of complex mixtures of organic compounds amenable to GC.[17] The technique uses two serially joined GC columns whereby effluent from the first is collected and periodically reinjected onto a second column in a process known as modulation (Figure 1).

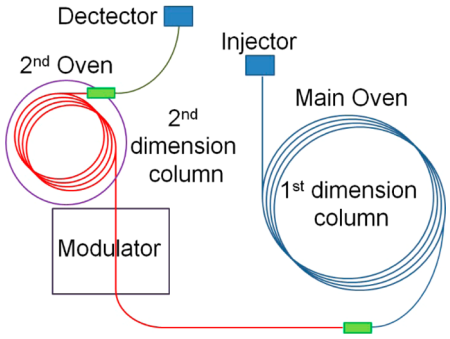
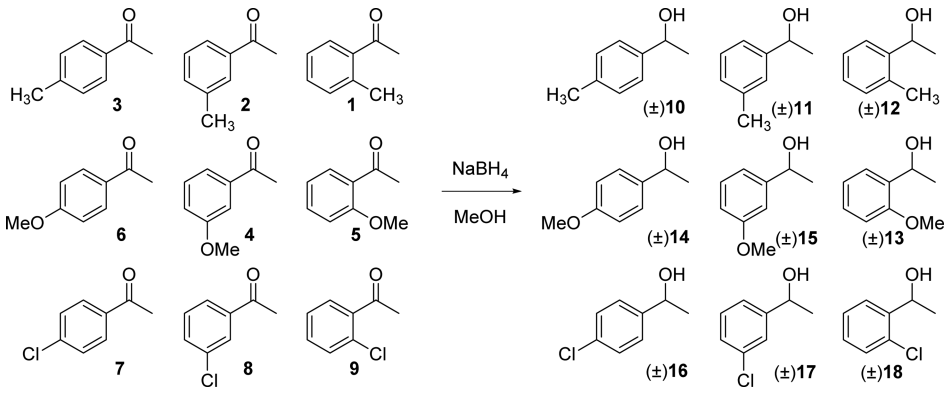


Figure 1. Instrument schematic of comprehensive two-dimensional gas chromatograph (GC×GC). The columns employed for GC×GC are identical to those used for one-dimensional GC (30−60 m); however, second-dimension column lengths are shorter (1−2 m). A cryogenically cooled thermal modulator utilizes cooled dry nitrogen to trap and focus effluent from the first dimension column at the thermal modulator. A jet of hot air is then used to desorb this focused effluent and launch it onto the second dimension column. Each "trap and release" is a modulation and all compounds for each modulation must be released.

The modulation cycle is sufficiently fast that all peaks eluting from the first column can be sampled multiple times (generally 3−4) and that all compounds eluted from the column before the next modulation. Hence, the term "comprehensive", in that all components injected onto the first column are also separated on the second column, setting this apart from decades long approaches using heart-cutting two-dimensional gas chromatography.[18] In this way, separation achieved in the first dimension is preserved and further separation is afforded by the second column. Depending on the choice of stationary phases, compounds can be separated by two different physical properties (e.g., boiling point and polarity), leading to groupings of chemical classes within a GC×GC chromatogram.[19] In combination with a time-of-flight mass spectrometer (TOF-MS), the enhanced resolution and increased signal-to-noise afforded by GC×GC allows for more accurate spectral identification of many compounds.[20,21] GC×GC has increasingly found a niche in complex hydrocarbon analysis for petroleum research and oil spill science,[22] but other applications have emerged primarily within the fields of environmental and atmospheric research.[23] Coupling of GC×GC with a flame ionization detector (FID) allows for the necessary separations but also the capacity to get reasonably accurate concentrations of every compound within the GC×GC chromatogram because most hydrocarbons have similar response factors.[24] With the incorporation of a chiral column into the first ("chiral-GC×GC") or second-dimension ("GC×chiral-GC"), enhanced resolution of enantiomers can be achieved, and has been reported for the analysis of chiral terpenes within plant extracts,[25] petroleum-contaminated marine sediments,[26] and more recently to study dynamic molecular interconversion processes.[27] However, both chiral-GC×GC and GC×chiral-GC remain fairly underdeveloped, perhaps restricted by the relatively low maximum temperature limits of standard chiral GC columns with GC×GC used primarily to study petroleum (maximum chiral GC column temperatures are generally ∼230−250 °C which would correspond to a limit of *n*-alkanes < $\sim C_{20}$).

Despite the exceptional analytical capability of GC×GC for many organic molecules, the technique has yet to be embraced by the synthetic organic community.[28] With improvements in processing software and the advent of GC×GC facilities available for sample submission, we argue that GC×GC has great potential for various applications within the many facets of synthetic organic chemistry. Here, we chose to investigate the use of chiral-GC×GC to analyze mixtures representing a substrate scope analysis of a classic transformation that nonetheless remains at the forefront of reaction development research: asymmetric ketone reductions. Asymmetric reductions account for more than half of all industrial asymmetric catalytic processes,[29] and earned Noyori and Knowles the Nobel Prize in chemistry for their contributions to the field. The work that followed Noyori's initial report of a ruthenium-BINAP catalyzed enantioselective reduction of *β*-ketoesters[30] is an excellent example of the advances that can and continue to result from methods development research. Improvements to the original procedure include in situ or simplified catalyst generation,[31] milder reaction

Scheme 1. Preparation of a Representative Pool of Analytes from an Asymmetric Ketone Reduction Substrate Scope Investigation



DOI: 10.1021/acs.joc.6b00050
J. Org. Chem. 2016, 81, 3533−3541

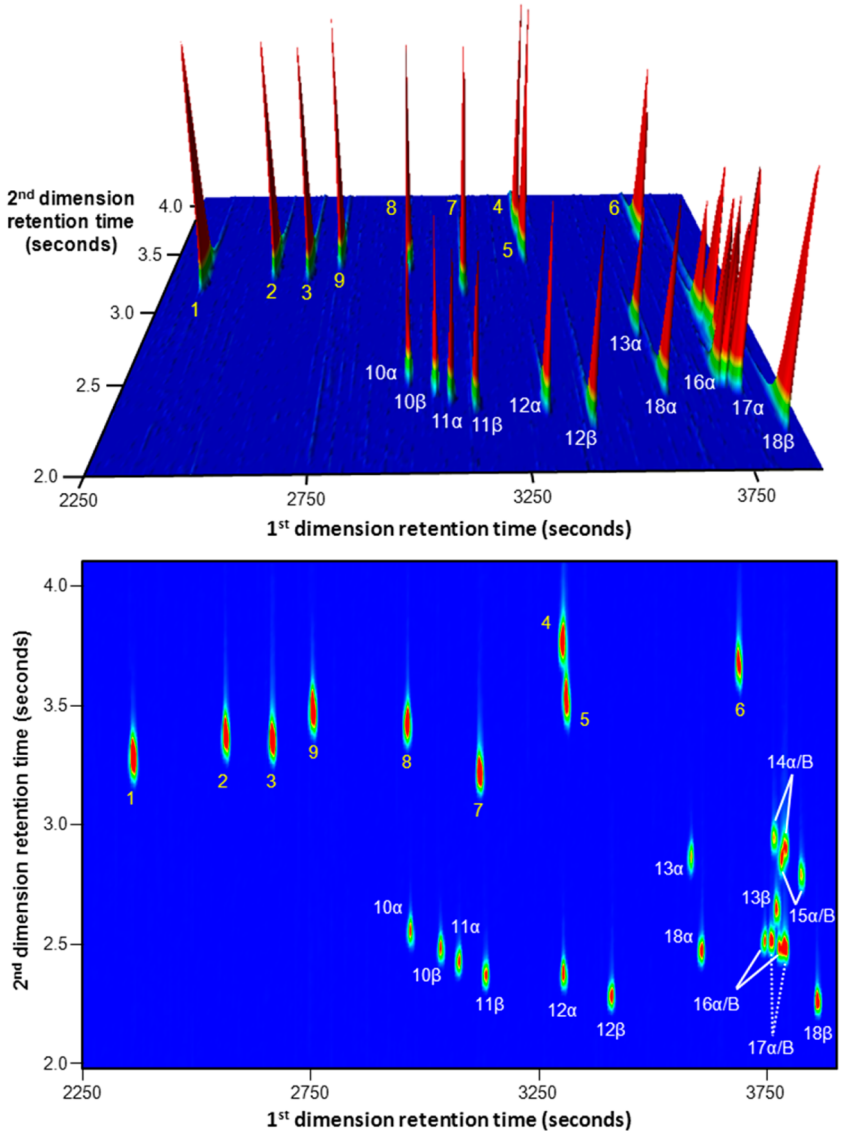


Figure 2. Two different projections of the chiral-GC×GC-TOF chromatogram of a mixture containing acetophenones **1**−**9** and reduced racemic products **10**−**18** shown as a "mountain plot" (top) and plan view (bottom). All 27 compounds are resolved and could be identified and quantified within the mixture, where α/β refer to enantiomer pairs. Note the substantial separation of acetophenones (**1**−**9**) and their more polar reduced products (**10**−**18**) in the second dimension due to the increased retention of the ketones on the second dimension column relative to the products. Enantioselective first dimension separations performed in this procedure were achieved using a 30 m Rt-bDEXsm (0.25 mm i.d., 0.25 μm df). Second dimension separations were accomplished on a 1.25 m SGE BPX-50 (0.10 mm i.d., 0.10 μm df) polar chromatographic phase. The hot pulse width was 0.75 s and the modulation period was 6 s. This means that analytes trapped and focused at the thermal modulator are injected onto the second column were they are chromatographically separated in 6 s intervals before reaching the TOF-MS detector.

conditions,[32] and the use of cheaper and greener metal catalysts.[33] As a recent example of the latter, Li et al. have described a new chiral iron-complex capable of catalyzing the enantioselective reduction of various aryl ketones in very high yield and enantioselectivities (entry 4, Table 1).[6] Suffice it to say, it is likely that this important reaction will continue to be the subject of numerous research efforts and was therefore chosen as a target for our one-pot/single-analysis approach.

RESULTS AND DISCUSSION

Table 2 in Li's report presents data from their substrate scope investigations including data for 20 different substituted acetophenones.[6] For our demonstration, we chose a sampling of substrates from this table: the methoxy-, chloro-, and methyl-; ortho-, meta-, and para-substituted acetophenones **1**−**9** (Scheme 1). These compounds are often found in substrate scope analyses of new reactions,[34] being commercially available and containing both electron-withdrawing (chloro) and electron-donating (methyl and methoxy) substituents. The acetophenones were reduced to their corresponding racemic alcohols **10**−**18** using sodium borohydride. Together, the 27 compounds (including enantiomers) represent a typical analyte pool for an enantioselective ketone reduction substrate scope analysis. Normally, the %conversion and ee for each of the substrates would be obtained by performing nine individual reactions on each of the acetophenones, with each product isolated, and analyzed separately. However, we sought to investigate the capabilities of chiral-GC×GC in resolving the entire mixture, making possible a rapid screening for this type of reaction development.

DOI: 10.1021/acs.joc.6b00050
J. Org. Chem. 2016, 81, 3533−3541

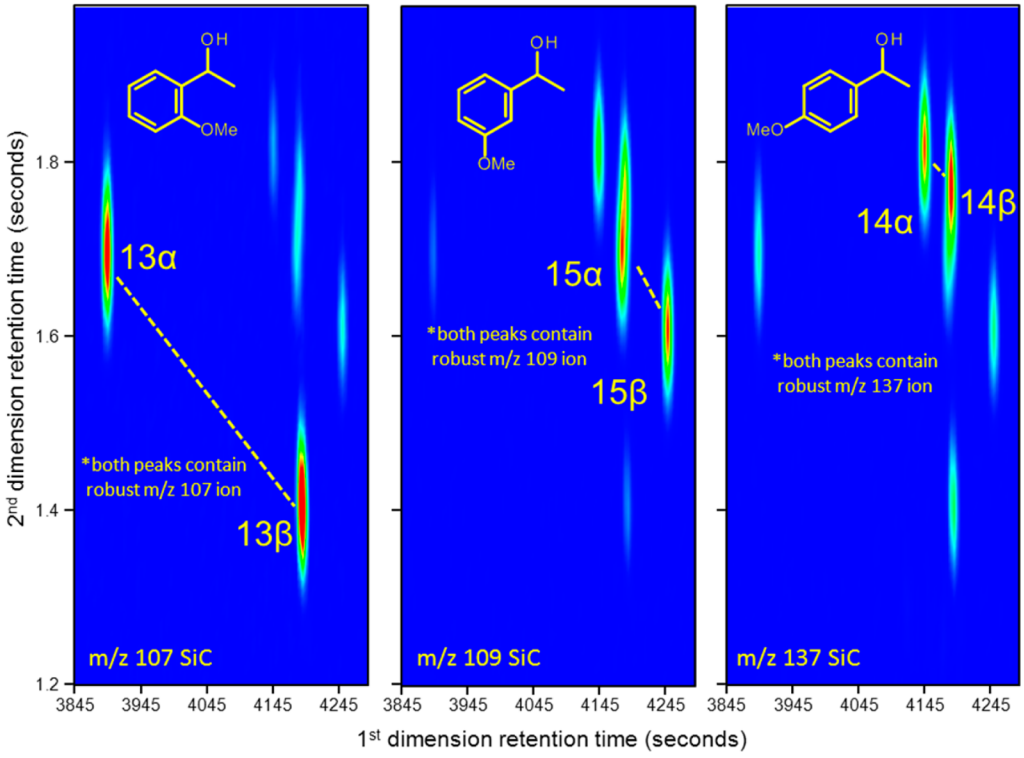


Figure 3. Selected ion chiral-GC×GC-TOF chromatograms (SiC) showing differentiation of the ortho-, meta-, and para-methoxy reduced acetophenone alcohol isomers based on their mass spectra. The ortho-substituted enantiomers **13α/β** exhibited an abundant m/z = 107 ion, whereas the meta-substituted enantiomers **15α/β** had an abundant m/z = 109 ion, and the para-substituted enantiomers **14α/β** had an abundant m/z = 137 ion.

Figure 2 shows two different views of a GC×GC-TOF chromatogram for the analysis of the same mixture containing acetophenones **1**−**9** and reduced racemic products **10**−**18** (refer to Scheme 1). This was obtained using a GC×GC instrument equipped with a chiral cyclodextrin-based first-dimension GC column (30 m, 0.25 mm i.d., 0.25 μm df) and polar second-dimension GC column (1.2 m, 0.10 mm i.d., 0.10 μm df). Of note is the dramatic separation between the starting acetophenones and their corresponding alcohol reduction products in the second dimension due to the large differences in polarity for these two classes of compounds. From this data, all of the components could be resolved, identified, and quantified.

Individual isomers were identified in some cases based on characteristic fragmentation patterns in their mass spectrum (e.g., within the methoxy-substituted series, the ortho-isomer exhibited a signature abundant m/z = 107 ion, the meta-isomer an abundant m/z = 109 ion, and para an abundant m/z = 137 ion, Figure 3). For others, the relative GC retention times of the different isomers were determined by analysis of pure compounds (e.g., the order of elution for the reduced methyl-substituted alcohol series was para < meta < ortho). Otherwise, pairs of enantiomers could also be identified knowing that their integrations would be 1:1 in the racemic sample, which proved to be a convenient solution to isomer assignments. As a demonstration, we purposely prepared a racemic mixture containing instead of equimolar amounts of the different compounds, a 1:2:4 molar ratio of the ortho-, meta-, and para-isomers. Analysis by chiral-GC×GC allowed for unambiguous assignment of the isomers based on their integration data (i.e., signal intensity for the ortho was smallest, meta middle, and para highest, Figure 4).

The GC×GC-TOF chromatogram in Figure 2 provides proof-of-concept for the use of chiral-GC×GC to streamline

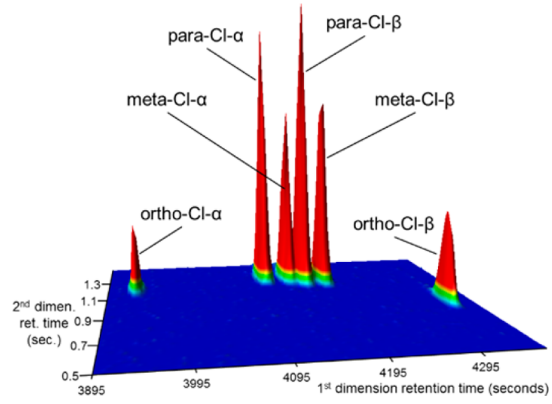


Figure 4. Enantiomeric pairs of isomers could be conveniently identified in the racemic sample based on their relative peak intensities using a mixture prepared by reduction of a 1:2:4 molar ratio of ortho/meta/para-acetophenones **1**−**9**. For example, the ortho-chloro substituted alcohol enantiomer products (**18α/β**) had the lowest intensity, meta-substituted (**17α/β**) had middle intensity, and para-substituted (**16α/β**) had the greatest intensity (bottom).

enantioselective ketone reaction development. Nonetheless, we wanted to test the effectiveness of this technique for analyzing a genuine complex mixture of compounds from an enantioselective reduction. It was thought that by interrogating a reaction using this mixed substrate approach, new insights might be revealed related to chemoselectivity and other possible synergistic effects.

In addition to the iron-catalyzed asymmetric hydrogenation referenced earlier from Li and co-workers,[6] this same group has also recently reported a similar iron-catalyzed asymmetric transfer hydrogenation (ATH) utilizing the same macrocyclic

DOI: 10.1021/acs.joc.6b00050
J. Org. Chem. 2016, 81, 3533−3541

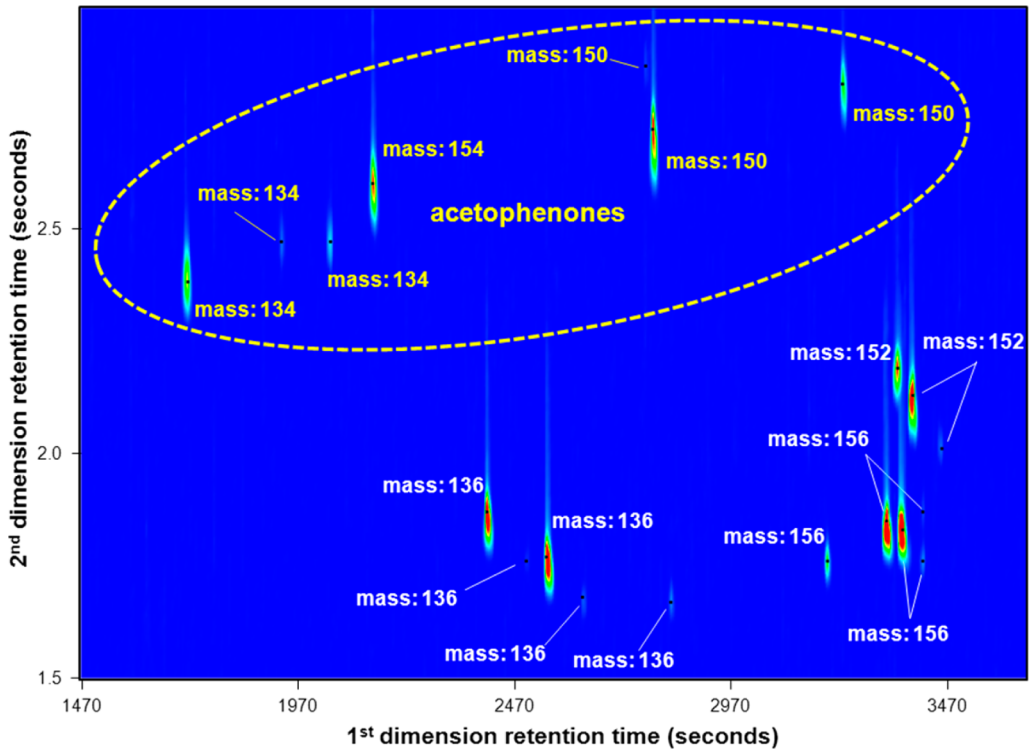


Figure 5. GC×GC-TOF chromatogram (plan view) from the one-pot $Fe_3(CO)_{12}$/**L1** ATH reaction of acetophenones **1**−**9** showing partial conversion for some substrates (where the largest peaks with mass = 134, 154, and 150 are unreacted ortho-methyl-, ortho-chloro-, and ortho-methoxy-substituted acetophenones **1**, **9**, and **5**, respectively) and enantioenriched products (MW = 136 (methyl-substituted), 152 (methoxy-substituted), and 156 (chloro-substituted)).

P_2N_4 ligand **L1** (refer to entry 4, Table 1).[35] The substrate scope portion of their study included results from individual ATH reactions of acetophenones **1**−**9** (refer to Scheme 1). We did a similar study, but in this case by performing a single reaction on an equimolar mixture of compounds **1**−**9** and analyzing the products by chiral-GC×GC. Figure 5 is the total ion GC×GC-TOF chromatogram of this ATH reaction mixture showing signals corresponding to unreacted acetophenones **1**−**6** and **9** along with reduced products **10**−**18**. A comparison of alcohol regions within chromatograms for the racemic mixture to this enantioenriched sample clearly illustrates the selectivity of this ATH process (Figure 6). The absolute configurations of the major products to be expected from these reactions were not reported by Li et al.;[35] however, similar asymmetric hydrogenations of compounds **1**−**9** using the same $Fe_3(CO)_{12}$/**L1** catalyst gave in all cases the (*S*)-alcohols as the major products.[6]

From the data contained in Figures 5 and 6, we calculated the %conversions for each of the acetophenones **1**−**9** along with the ee for reduced products **10**−**18**. This data is presented in Table 2 along with previously reported data for the same ATH reaction performed individually on acetophenones **1**−**9**.[35] Care should be taken, however, when comparing the data directly, as the individual reactions were optimized for that particular substrate (i.e., temperatures from 55 to 75 °C for 0.5−2 h). Nonetheless, several salient observations can be made. Consistent with the data from individualized reactions, the lowest %conversions were observed for ortho-substituted acetophenones (**1**, **5**, and **9**) and highest for the meta- and para-chloro acetophenones **7** and **8** in the mixture. Additionally, in both studies, the ortho-methyl substituted acetophenone **1** was the least reactive (15% at 65 °C for 30 min (one-pot) vs 64% at 75 °C for 2 h (individual)). As might be expected, while ortho-substituted acetophenones gave the lowest %conversions, the corresponding products were obtained with the highest enantioselectivity. For each of the ortho-isomers, none of the other enantiomer was detected. The detection limits for all of the compounds studied were determined to be 500 pg on column or lower and signal was linear up to 20 ng.[36] The results presented in Table 2 are bounded within this mass range. In general, the results align fairly well. This is not only a testament to the reproducibility of the reaction and the potential value of this one-pot/GC×GC approach toward methods development, but also an indication for this particular system that the presence of other acetophenones or enantioenriched reduced products does not greatly effect catalyst performance. There are reports of reactions that display so-called enantioselective autoinduction,[37−39] where a product participates in the formation of a new chiral catalyst that exhibits different enantioselectivities than the original metal complex. It is possible that a reinvestigation of other catalytic asymmetric methods performed as a single reaction on a multiple-substrate mixture may uncover autoinduction-type or other effects and in the process better our understanding of these transformations.

CONCLUSION

We have demonstrated the usage of chiral-GC×GC to greatly streamline substrate scope analyses for new reaction development as well as the opportunity to confirm, refine, and explore new aspects of previously reported catalytic systems. Specifically, the substrate scope portion of a recently reported asymmetric transfer hydrogenation could be condensed to a single reaction performed on an equimolar mixture of substrates owing to the greater resolving capabilities of GC×GC. Aside from being significantly less resource intensive and therefore a "greener"

DOI: 10.1021/acs.joc.6b00050
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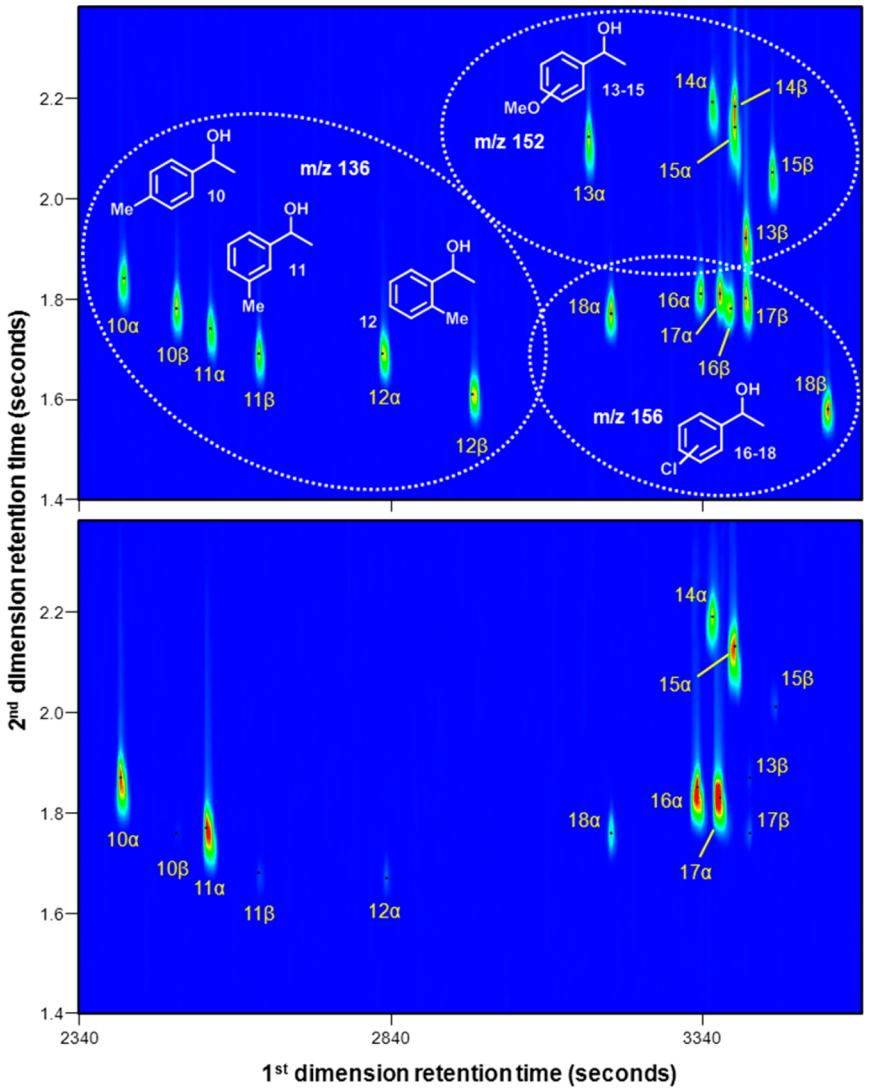

Figure 6. Reduced acetophenone regions of GC×GC-TOF chromatograms from a nonselective reduction ($NaBH_4$) containing a racemic mixture of compounds (top) and enantioenriched alcohols produced by an Fe/**L1** ATH reaction (bottom). A comparison of these chromatograms clearly indicates the selectivity achieved by this ATH reaction (e.g., relative intensities of enantiomers 10*α* vs 10*β*, 11*α* vs 11*β*, etc.).

Table 2. Comparison of Results from Fe/L1 ATH Reactions Performed on Individual Substituted Acetophenones (Yu et al.) and an Equimolar Mixture of Acetophenones (One-Pot/Single Chiral-GC×GC Analysis)

one-pot/single chiral-GC×GC analysis[a]			Yu et al. (individual reactions)		
acetophenone	%ee	%conversion	temp./time	%ee	%conversion
ortho-Me (**3**)	>99[b]	15.1	75 °C, 2 h	99	64
meta-Me (**2**)	92.8	98.0	55 °C, 1 h	96	92
para-Me (**1**)	95.6	94.5	75 °C, 0.5 h	96	94
ortho-Cl (**9**)	>99[b]	47.1	75 °C, 2 h	97	92
meta-Cl (**8**)	91.5	100	55 °C, 0.5 h	95	98
para-Cl (**7**)	>99[b]	100	65 °C, 0.5 h	97	99
ortho-OMe (**5**)	>99[b]	4.8	--	ND[d]	ND[d]
meta-OMe (**4**)	89.2	97.7	55 °C, 1 h	92	91
para-OMe (**6**)	>95[c]	66.0	75 °C, 0.5 h	93	86

[a]The reaction was performed on a 1 mmol mixture of acetophenones **1**–**9** (1/9 mmol each acetophenone), $Fe_3(CO)_{12}$ (0.5 mol %), **L1** (0.5 mol %), NH_4Cl (6 mol %), KOH (12 mol %), and *i*-PrOH (10 mL) at 65 °C for 30 min. [b]The other enantiomer was not detected. [c]Trace amounts were observed in the mass spectrum based on signature fragmentation patterns (see Supporting Information). [d]ND = not determined.

approach to methods development, this one-pot strategy enabled by GC×GC also represents a new angle with which to examine various catalytic reactions. For instance, the ATH reaction used in this study gave similar results from the one-pot reaction with those reported for the individual substrates suggesting that the reactivity profile for this particular catalyst was not greatly

DOI: 10.1021/acs.joc.6b00050
J. Org. Chem. 2016, 81, 3533−3541

affected by a reaction medium containing other acetophenones or enantioenriched reduced products. It is possible, however, that one-pot mixed-substrate/GC×GC investigations may reveal certain chemoselectivity or other potential synergistic aspects of a given catalyst system that would otherwise not be apparent from traditional substrate scope studies. Additionally, the broad analytical plane afforded by GC×GC and presumably other two-dimensional chromatographic techniques[40] could lead to the identification of other unexpected products that may drive the next round of optimizations and innovations.

EXPERIMENTAL SECTION

Comprehensive Two-Dimensional Gas Chromatography (GC×GC). The GC×GC-TOF instrument used in this study was equipped with a GC configured with a split/splitless autoinjector and a dual stage cryogenic modulator. Samples were injected in splitless mode. The thermal modulator operates with a cold and hot jet. The cold jet gas was dry N_2 chilled with liquid N_2. The hot jet temperature offset was 20 °C above the temperature of the main GC oven and the inlet temperature was isothermal at 185 °C. Two capillary GC columns were utilized in this GC×GC experiment. The first-dimension column was a Rt-bDEXsm, (30 m length, 0.25 mm i.d., 0.25 μm df) and the second-dimension separations were performed on a 50% phenyl polysilphenylene−siloxane column (SGE BPX50, 1.2 m length, 0.10 mm i.d., 0.1 μm df).

GC×GC-TOF Method. The temperature program of the main oven started isothermal at 100 °C (15 min) and was then ramped from 100 to 200 °C at 1.25 °C min^{-1}. The hot jet pulse width was 0.75 s and the modulation period was 6.00 s with a 2.25 s cooling period between stages. The second dimension oven was programmed from 105 °C (15 min) to 205 °C at 1.25 °C min^{-1}. TOF-MS data was sampled at an acquisition rate of 100 spectra per second in the mass range of 40−400 amu. The transfer line from the second oven to the TOF-MS was deactivated fused silica (0.5 m length, 0.18 mm i.d.), constantly held at 310 °C. The TOF detector voltage was 1355 V and the source temperature 240 °C. The mass spectrometer employs 70 eV electron ionization and operates at a push pulse rate of 5 kHz allowing sufficient signal averaging time to ensure good signal-to-noise ratios while still operating at a high enough data acquisition rate to accurately process (signal average) spectra from the peaks eluting from the second dimension column in this high resolution separation technique (GC×GC-TOF second dimension peak widths range between 50 and 100 ms). Detector response for our TOF data was linear, and the measured ranges were 0.4−50 ng of component per injection.

GC×GC Interpretation. GC×GC produces a chromatogram that has a first dimension retention time, a second dimension retention time, and peak amplitudes (amplitude s^{-1} s^{-1}) from the TOF. For each peak, the abscissa is the retention time in the first column and the ordinate is the retention time in the second column. The number of pixels is the area of the peak and the sum of the pixels is the volume of the peak.[41] To quantify the specific amounts of each component in the acetophenone reduction mixture, we chose select ions that were unique to specific enantiomer pairs in cases where peaks were eluting in close proximity to one another (see data table in Supporting Information). For example, the para- and meta-methoxy reduced alcohol products labeled 14β and 15α nearly coelute. However, these compounds can be distinguished from one another and their volumes accurately quantified using m/z 109 and m/z 137 mass spectral ions, respectively (m/z 109 ion is abundant for the 15α meta-enantiomer, while the m/z 137 ion is abundant for the 14β para-enantiomer).

Enantioselective ATH Reaction.[29] A stock solution containing equimolar amounts of acetophenones **1**−**9** was first prepared by combining 1.11 mmol of each ketone into a single vial. The resulting mixture was a viscous oil with a total volume of 1.02 mL. To this mixture was then added isopropyl alcohol (8.98 mL) to produce a 1.0 M solution.

A dry Schlenk tube under nitrogen atmosphere was charged with $Fe_3(CO)_{12}$ (2.6 mg, 0.005 mmol, 0.005 equiv), NH_4Cl (3.2 mg, 0.06 mmol, 0.06 equiv), and chiral ligand **L1** (4.0 mg, 0.005 mmol, 0.005 equiv). Isopropyl alcohol (9.0 mL) was then added and the solution was stirred at 65 °C for 30 min. KOH (0.12 M in iPrOH, 1.0 mL, 0.12 mmol, 0.12 equiv) was then added, and the mixture was stirred for another 10 min. The mixed ketone solution (1.0 mL, 1.0 mmol, 1.0 equiv) was then added and the mixture was stirred for 1 h. The reaction was then cooled to room temperature, filtered through silica gel (5 g) with ethyl acetate (25 mL, R_f of compounds **1**−**18** = 1.0) using pressure (~5 psi), and concentrated in vacuo to give an oil (0.13 g, 91%) that was then analyzed by GC×GC.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00050.

GC×GC-TOF data for the Fe/**L1** ATH reaction of compounds **1**−**9**, linear regression curves for detection limits of compounds **10**−**18** by GC×GC, mass spectra for compounds **1**−**18** (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Science Foundation (CHE-1151492) and the Dreyfus Foundation is gratefully acknowledged. The authors thank J.-X. Gao for providing ligand **L1** used for our ATH reaction. We wish to thank Jack Cochran of the Restek Corporation for generously providing the 30-meter RT-bDEXsm gas chromatography column used in this manuscript.

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