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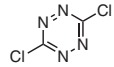
(1) Brown, S. P.; Smith, A. B., III. *J. Am. Chem. Soc.* **2015**, *137*, 4034. (2) Courter, J. R.; Abdo, M.; Brown, S. P.; Tucker, M. J.; Hochstrasser, R. M.; Smith, A. B., III. *J. Org. Chem.* **2014**, *79*, 759. (3) Tucker, M. J.; Abdo, M.; Courter, J. R.; Chen, J.; Brown, S. P.; Smith, A. B., III; Hochstrasser, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 17314.



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ABOUT OUR COVER

Detail from ***A Royal Party Admiring the Sunset atop the Hesselberg Mountain***. Photo courtesy National Gallery of Art, Washington, DC.

Johann Georg von Dillis (1759–1841), a German master painter of the late 18th and early 19th centuries, painted and signed ***A Royal Party Admiring the Sunset atop the Hesselberg Mountain*** in 1801. He received his first drawing lessons while attending the Gymnasium in Munich. He then studied art at the Munich Zeichnungsakademie under the guidance of F. I. Oefele and J. J. Dorner the Elder. His art career began ca. 1786 and, until his retirement in the late 1830s, consisted of official appointments by the courts of Maximilian I and Ludwig I, commissioned sketches and drawings, and a professorship of landscape painting at the Munich Royal Academy of Fine Arts. He travelled frequently and widely throughout Europe on Bavarian State business, and it was during these travels that he became acquainted with, and influenced by, the work of P.-H. de Valenciennes, S. Denis, J.-J.-X. Bidauld, W. Allston, and, especially, J. M. W. Turner. His artwork influenced such artists as C. E. F. Blechen, and his gallery work had a profound influence on the world of art in Germany, especially in Bavaria.

Von Dillis excelled at landscapes, and was instrumental in moving the genre from the classical tradition of idealized pastorals to a new, realistic form, whereby the artist draws from life, not only what he perceives with his eyes upon close examination of nature, but also what he feels within himself. This romantic approach to landscape painting values emotions, which are aroused nowhere better than in the countryside with its powerful pull on the artist, as this work demonstrates. Not only is the average person drawn to nature, but even sophisticated, urban dwellers such as this elegantly attired group of royals* and their aides can appreciate the wonders of nature. This composition (watercolor, gouache, and pen and gray ink over graphite on laid paper) measures 37 x 42.7 cm and is von Dillis's best-known work. With its crisp colors, decidedly finished look, and the artist's meticulous attention to detail, it clearly highlights von Dillis's complete immersion in the work.

This painting is part of the Wolfgang Ratjen Collection at the National Gallery of Art, Washington, DC.

** Who could the "royals" depicted in this painting be? To help solve the mystery, visit* ***Aldrich.com/acta482***

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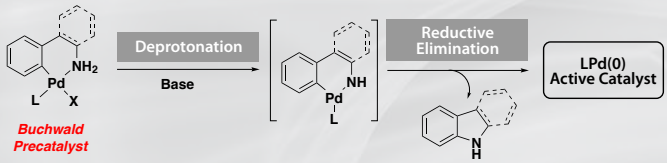

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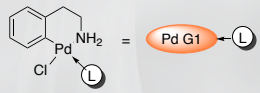

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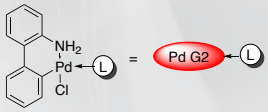

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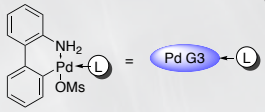

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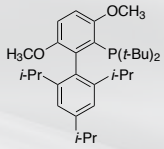

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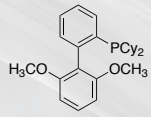

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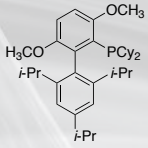

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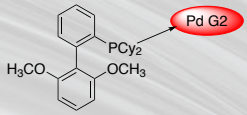

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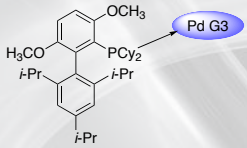

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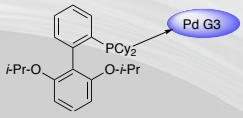

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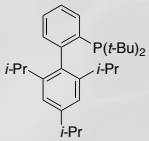

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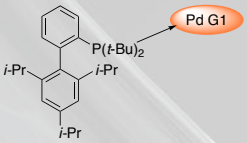

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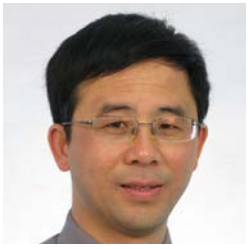
Catalytic Asymmetric Hydrogenation of α-Substituted Ketones and Aldehydes via Dynamic Kinetic Resolution: Efficient Approach to Chiral Alcohols



Prof. J.-H. Xie

Prof. Q.-L. Zhou

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Keywords. aldehydes; asymmetric hydrogenation; asymmetric synthesis; catalysis; chiral alcohols; dynamic kinetic resolution (DKR); ketones; natural product; pharmaceutical; ruthenium; spiro catalyst.

Abstract. The catalytic asymmetric hydrogenation of racemic α-substituted aldehydes or ketones via dynamic kinetic resolution (DKR) affords a highly efficient method for the preparation of chiral alcohols with one or more stereogenic centers. This review presents and discusses recent advances and applications of this approach.

Outline

1. Introduction

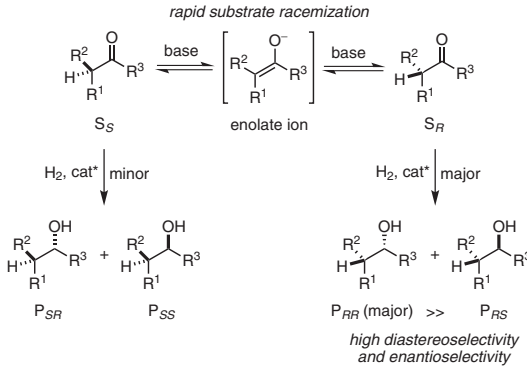
The catalytic asymmetric hydrogenation of α-substituted ketones via dynamic kinetic resolution (DKR) is a highly efficient method for obtaining optically active alcohols with two or more contiguous stereogenic centers in a single operation.[1] This method was first disclosed in 1996 by Noyori and co-workers, who reported the hydrogenation of racemic α-isopropylcyclohexanone with chiral $RuCl_2$[diphosphine]-[diamine] complexes as catalysts.[2] Soon thereafter, Matsumoto et al. applied this approach to the synthesis of the tricyclic β-lactam antibiotic sanfetrinem, highlighting the synthetic utility of the reaction.[3] Nevertheless, the application of the reaction in organic synthesis remained limited because only conformationally rigid substrates such as α-substituted cycloalkanones could provide the corresponding chiral alcohols with high enantioselectivity and diastereoselectivity.[1b] The challenge has been to find catalysts that selectively catalyze the hydrogenation of only one of the two enantiomers of the substrate, which can rapidly racemize via the corresponding enolate ion under the reaction conditions (**Scheme 1**).

We have explored the application of chiral spiro ruthenium complexes as catalysts for the asymmetric hydrogenation of racemic α-substituted aldehydes and ketones via DKR for the purpose of synthesizing optically active chiral alcohols. We found that $RuCl_2$[SDPs]-[diamine] complexes (**Figure 1**)[4] efficiently catalyze the reaction of both conformationally rigid and flexible substrates. This work led to the development of several new methods for the preparation of optically active primary alcohols with one stereocenter[5] and secondary alcohols with two or three contiguous stereocenters.[6] These methods not only provide a practical and environmentally benign route to chiral alcohols, but they also facilitate the enantioselective synthesis of chiral pharmaceuticals and biologically active natural products. This review focuses on recent progress in the enantioselective synthesis of diverse chiral alcohols and their applications in the enantioselective synthesis of chiral pharmaceuticals and natural products.

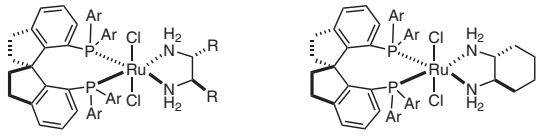
2. Asymmetric Hydrogenation via DKR

2.1. α-Substituted Aldehydes to Chiral Primary Alcohols

Although the catalytic asymmetric hydrogenation of prochiral ketones is a powerful method for the synthesis of chiral secondary alcohols, the asymmetric hydrogenation of racemic α-substituted aldehydes to form chiral primary alcohols had remained a challenge until recently. This has been the case mainly because no new stereogenic center is generated in the hydrogenation of α-substituted aldehydes, which makes enantiocontrol of the reaction extremely difficult. In this respect, the ideal synthesis of chiral primary alcohols would involve asymmetric hydrogenation of racemic α-substituted aldehydes via DKR. In 2007, we reported the first examples of such a reaction catalyzed by chiral spiro ruthenium catalysts.[7] For example, in the presence of $RuCl_2$[(S_a)-DMM-SDP][(*R*,*R*)-DACH] (**2a**, 0.1 mol %) and a base (KO*t*-Bu, 20 mol %) under 50 atm of hydrogen, various racemic α-aryl aldehydes were hydrogenated to chiral primary alcohols with 100% conversion and 78–96% enantiomeric excess (ee) (**eq 1**).[7] Substrates with a bulky α-alkyl group in addition to the α-aryl group gave higher enantioselectivities.



Scheme 1. Asymmetric Hydrogenation of Racemic Ketones and Aldehydes via DKR.



$RuCl_2[(S_a)\text{-SDP}][(R,R)\text{-DPEN}]$ (**1**)

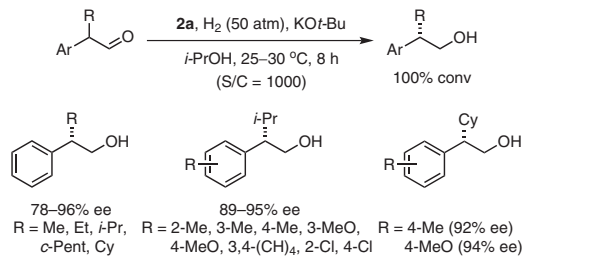
R	Ar	No
H	3,5-Me_2-4-$MeOC_6H_2$ (DMM)	**1a**
Ph	4-Tol (Tol)	**1b**
Ph	Ph	**1c**
Ph	3,5-$Me_2C_6H_3$ (Xyl)	**1d**

$RuCl_2[(S_a)\text{-SDP}][(R,R)\text{-DACH}]$ (**2**)

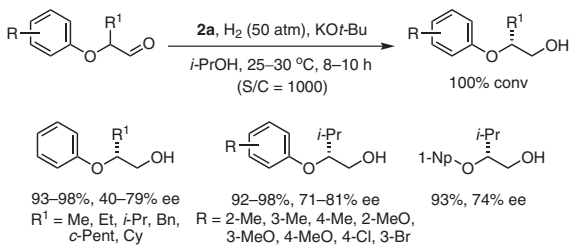
Ar	No
3,5-Me_2-4-$MeOC_6H_2$ (DMM)	**2a**
3,5-$Me_2C_6H_3$ (Xyl)	**2b**

SDP = spiro diphosphine; DPEN = 1,2-diphenylethylenediamine;
DACH = *trans*-1,2-diaminocyclohexane

Figure 1. Chiral Spiro Ruthenium Complexes Employed as Effective Catalysts of the Asymmetric Hydrogenation of Racemic α-Substituted Aldehydes and Ketones via DKR. *(Ref. 4–6)*



eq 1 *(Ref. 7)*



eq 2 *(Ref. 8)*

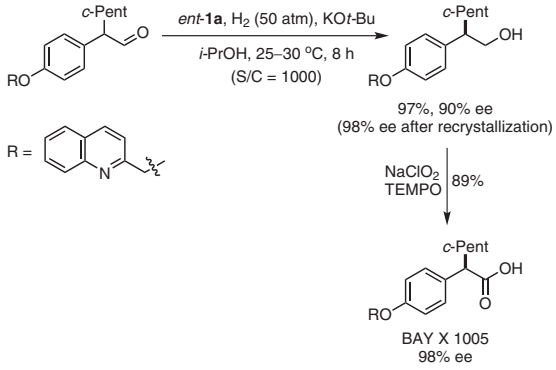
However, the location and the electronic nature of the substituent on the aromatic ring of the substrate has little impact on the enantioselectivity.

With the same catalyst, **2a**, racemic α-aryloxy aldehydes could also be hydrogenated to the corresponding chiral β-aryloxy primary alcohols with moderate-to-good enantioselectivities (**eq 2**).[8] As was the case for α-aryl aldehydes, α-aryloxy aldehydes with a bulky α-alkyl group, such as isopropyl, resulted in higher enantioselectivities.

List[9] and Lin[10] have achieved highly efficient and enantioselective hydrogenations of racemic α-aryl aldehydes to chiral primary alcohols via DKR by employing Noyori BINAP catalysts $RuCl_2[(S_a)$-Xyl-BINAP$][(S,S)$-DACH] and $RuCl_2[(R_a)$-Xyl-BINAP$][(R,R)$-siloxy-DACH]. The chiral primary alcohols produced by this reaction are highly useful for organic synthesis. For example, (*S*)-2-(4-methoxyphenyl)-3-methylbutan-1-ol is a key intermediate in the preparation of (1*S*,4*S*)-*cis*-7-methoxycalamenene,[11] and (*S*)-2-(4-chlorophenyl)-3-methylbutan-1-ol can be easily converted into (*S*)-2-(4-chlorophenyl)-3-methylbutanoic acid, which is a building block for the pyrethroid pesticide (*S*,*S*)-fenvalerate.[12] We have used this reaction to synthesize BAY X 1005, a leukotriene receptor antagonist and a potent inhibitor of lipoxygenase activating protein,[13] in only a few steps (**Scheme 2**).[7]

2.2. Alkyl Ketones with an α-Aryl Substituent to Chiral Secondary Alcohols with Two Stereogenic Centers

The catalytic asymmetric hydrogenation via DKR of racemic alkyl ketones possessing an α-aryl substituent is an efficient method for the synthesis of chiral secondary alcohols with two adjacent stereogenic centers. Because cycloalkanones are more conformationally rigid than acyclic alkanones, the asymmetric hydrogenation of racemic α-aryl cycloalkanones via DKR has received more attention than similar reactions of acyclic ketones. For example, in 2003, Scalone and Waldmeier reported an efficient asymmetric hydrogenation of dibenzylpiperidin-3-one catalyzed by $RuCl_2[(S_a)$-3,5-^{i}Pr-MeOBIPHEP$]$-$[(R,R)$-DPEN]. The reaction afforded chiral *cis*-1,4-dibenzylpiperidin-3-ol with 96% ee and 99% cis-selectivity. These investigators applied this method to the synthesis of Ro 67-8867, an NMDA 2B receptor antagonist that has potential for the treatment of acute ischemic stroke.[14] In 2004, Noyori and co-workers reported the hydrogenation of racemic α-arylcycloalkanones catalyzed by $RuCl_2[(S_a)$-Tol-BINAP$]$-$[(S,S)$-DPEN] to give chiral *cis*-β-arylcycloalkanols with excellent enantioselectivities (up to 99.7% ee) and cis:trans selectivities (≥98:2).[15]



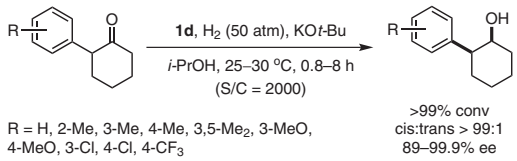
Scheme 2. Application of the Enantioselective Hydrogenation of Racemic α-Aryl Aldehydes via DKR to the Enantioselective Synthesis of BAY X 1005. *(Ref. 7)*

We have also studied the asymmetric hydrogenation of racemic α-arylcyclohexanones for the purpose of developing new strategies for the asymmetric total synthesis of chiral natural products. We found that $RuCl_2[(S_a)$-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) efficiently catalyzed the asymmetric hydrogenation of racemic α-arylcyclohexanones, yielding *cis*-β-arylcyclohexanols in 89–99.9% ee and cis:trans selectivities of >99:1 (**eq 3**).[16] An electron-donating or withdrawing group at the meta or para position of the benzene ring of the substrate has little influence on the enantioselectivity, but a substrate with an ortho substituent gave lower enantioselectivity. This catalyst could also be used for cycloalkanones possessing a five- or seven-membered ring, although the resulting enantioselectivities were lower.

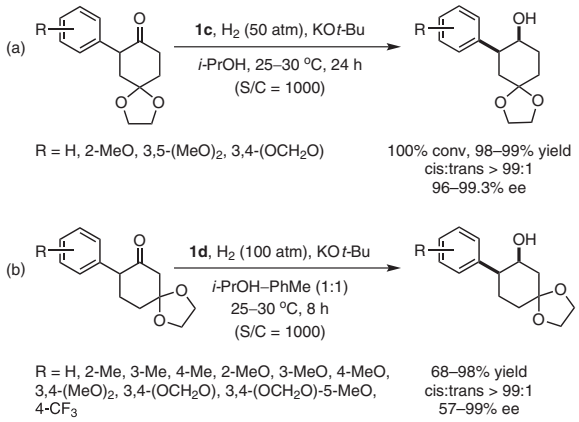
These results encouraged us to study the asymmetric hydrogenation of racemic α-arylcyclohexanones with a bulky ethylene ketal group attached to the cyclohexanone ring. The ketal-functionalized chiral β-arylcyclohexanols that would result are potential chiral building blocks for the synthesis of bioactive natural products and chiral drugs. The hydrogenation proceeded well in the presence of $RuCl_2[(S_a)$-SDP][(*R*,*R*)-DPEN] (**1c**) as catalyst, and led to the corresponding chiral *cis*-β-arylcyclohexanols in excellent yields and up to 99.3% ee (**Scheme 3**, Part (a)).[17] One exception was the cyclohexanone with a 2,6-dimethoxyphenyl substituent at C2, which gave only 5% conversion. In contrast, substrates with the ketal group at the 5 position gave nearly quantitative yields of 3-isopropoxy-2-cyclohexenones instead of the desired products. However, after careful optimization of the reaction conditions, we found that these base-sensitive α-arylcyclohexanones could be catalytically hydrogenated with $RuCl_2[(S_a)$-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) (in a 1:1 (v/v) mixture of isopropanol and toluene under 100 atm of H_2) to afford chiral *cis*-β-arylcyclohexanols in good-to-excellent yields (68–98%), high enantioselectivities (up to 99% ee), and very high cis:trans selectivities (>99:1) (Scheme 3, Part (b)).[18]

The asymmetric hydrogenation of racemic α-arylcyclohexanones via DKR is a highly efficient method for the construction of chiral, aryl-substituted cyclohexane motifs, and has been applied to the asymmetric total syntheses of various natural products and pharmaceuticals (**Scheme 4**). For example, the cannabinoids (–)-Δ^8-THC and (–)-Δ^9-THC, isolated from *Cannabis sativa* L.,[19] share a chiral hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene motif, which can be constructed by the catalytic asymmetric hydrogenation of racemic 7-aryl-1,4-dioxaspiro[4.5]decan-8-one and subsequent intramolecular S_NAr cyclization. We have synthesized these two aromatic terpenoids in 35% and 30% overall yields in 13 and 14 steps, respectively, from commercially available starting materials.[20] Similarly, (–)-CP-55940, a potent nonselective cannabinoid (CB) receptor agonist for human recombinant CB1 and CB2 receptors,[21] has been synthesized in 14% yield over 14 steps.[17] Furthermore, by employing the product of the hydrogenation of racemic 8-aryl-1,4-dioxaspiro[4.5]decan-7-one as a key chiral intermediate, we have synthesized (–)-α-lycorane, a pentacyclic alkaloid isolated from plants of the amaryllidaceae family, in 19.6% yield over 13 steps from commercially available 1,4-dioxaspiro[4.5]decan-7-one.[18]

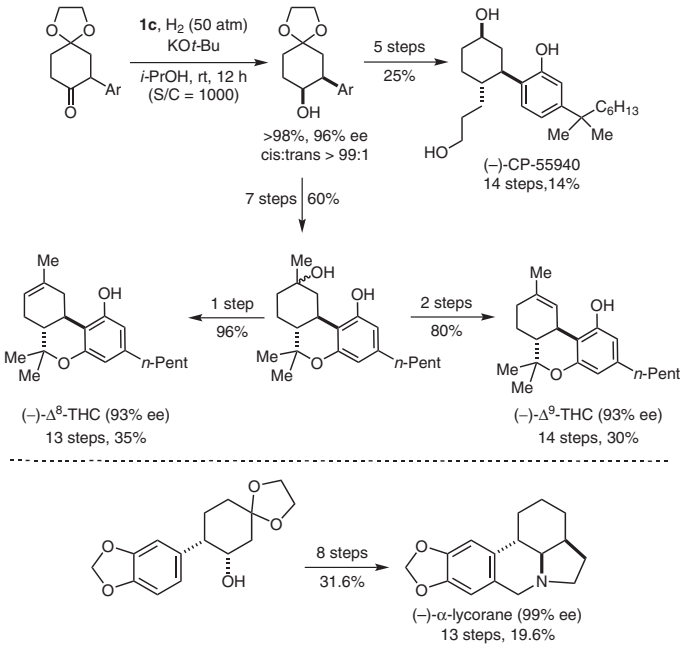
Chiral 1-alkyl-1-aryl-2-propanols are important building blocks for the preparation of chiral drugs. In 2007, Chen and co-workers reported that chiral $RuCl_2$[diphosphine][diamine] complexes efficiently catalyze the hydrogenation of racemic 1-alkyl-1-aryl-2-propanones via DKR to afford chiral alcohols.[22] For example, the asymmetric hydrogenation of racemic 3-(3-bromophenyl)-4-(4-chlorophenyl)-2-butanone catalyzed by $RuCl_2[(S_a)$-Xyl-BINAP][(*S*)-DAIPEN] (DAIPEN = 1-isopropyl-2,2-bis(4-methoxyphenyl)ethylenediamine) yielded the corresponding chiral alcohol with 95% ee but with lower diastereoselectivity



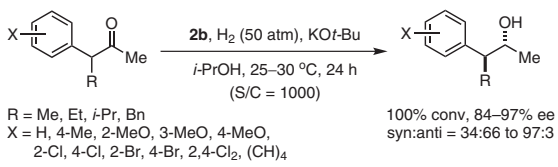
eq 3 *(Ref. 16)*



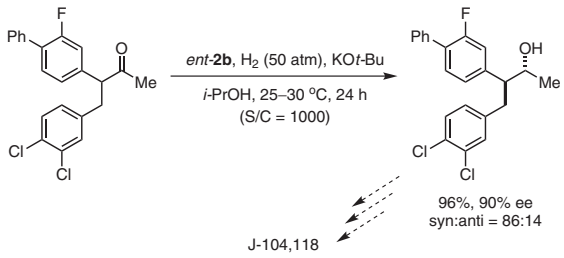
Scheme 3. Enantioselective Hydrogenation of Racemic 7-Aryl-1,4-dioxaspiro[4.5]decan-8-ones and 8-Aryl-1,4-dioxaspiro[4.5]decan-7-ones. *(Ref. 17,18)*



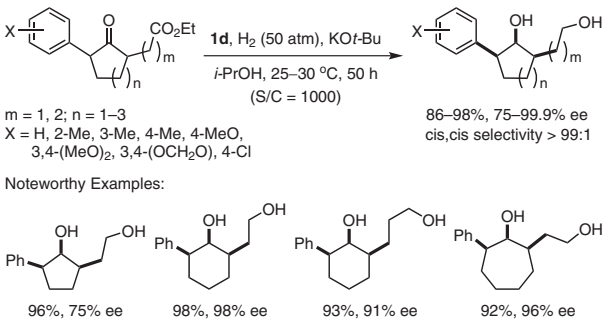
Scheme 4. Application of the Catalytic Asymmetric Hydrogenation of α-Substituted Ketones to the Enantioselective Synthesis of (–)-CP-55940, (–)-Δ^8-THC, (–)-Δ^9-THC, and (–)-α-Lycorane. *(Ref. 17,18,20)*



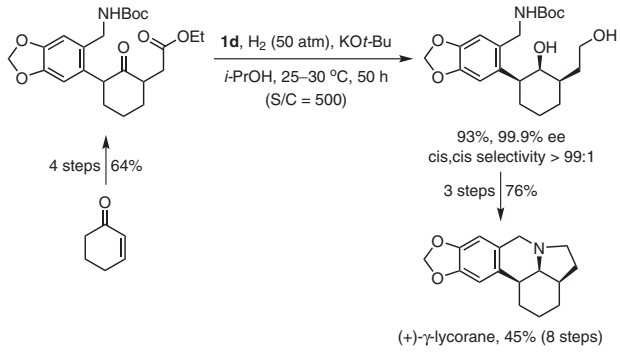
eq 4 *(Ref. 24)*



Scheme 5. Enantioselective Synthesis of Key Intermediate in the Synthesis of Squalene Synthase Inhibitor J-104,118. *(Ref. 24)*



eq 5 *(Ref. 6)*



Scheme 6. Enantioselective Synthesis of the Amaryllidaceae Alkaloid (+)-γ-Lycorane. *(Ref. 6)*

(syn:anti = 8:1). Higher diastereoselectivity (syn:anti up to 23:1) could be achieved with $RuCl_2[(R_a)$-Xyl-PhanePhos][(*S,S*)-DPEN] (Xyl-PhanePhos = 4,12-bis(di-3,5-xylylphosphino)[2.2]paracyclophane), but the enantioselectivity was lower (88% ee). Although this method has been employed in the synthesis of MK-0346, an oral inverse agonist for the CB1 receptor,[23] the asymmetric hydrogenation of conformationally flexible, racemic, and acyclic α-substituted dialkyl ketones via DKR has remained a challenge.

We have investigated the use of $RuCl_2$[SDP][diamine] catalysts for the asymmetric hydrogenation of conformationally flexible racemic dialkyl ketones via DKR.[24] After careful evaluation of various catalysts, $RuCl_2[(S_a)$-Xyl-SDP][(*R,R*)-DACH] (**2b**) was found to be the best choice for the hydrogenation of racemic 1-alkyl-1-aryl-2-propanones via DKR, producing chiral 1-alkyl-1-aryl-2-propanols in high yields, good-to-excellent enantioselectivities (84–97% ee), and diastereoselectivities (syn:anti up to 97:3) (**eq 4**).[24] The α-alkyl group strongly influenced the enantioselectivity and diastereoselectivity: higher enantioselectivities and diastereoselectivities were obtained with α-benzyl ketones. The electronic nature of the substituent on the phenyl ring had no obvious effect on either the enantioselectivity or the diastereoselectivity. However, benzylic substrates with ortho substituents on the phenyl ring gave relatively higher enantioselectivity and diastereoselectivity.

The asymmetric hydrogenation of a fluorinated racemic α-benzyl 1-aryl-2-propanone catalyzed by $RuCl_2[(R_a)$-Xyl-SDP][(*S,S*)-DACH] (*ent*-**2b**) was utilized to prepare a key intermediate in the synthesis of squalene synthase inhibitor J-104,118[25] (**Scheme 5**).[24]

Many natural products, such as γ-lycorane,[26] hexahydroapoerysopine,[27] and lycorine-type alkaloids,[28] contain a cyclic alcohol featuring three contiguous stereocenters. The asymmetric hydrogenation of racemic α,α'-disubstituted ketones via DKR offers a potential synthetic approach to this unit. However, since these ketones have four stereoisomers, controlling the enantio- and diastereoselectivity of their hydrogenation is extremely difficult. To address this challenge, we have investigated the asymmetric hydrogenation of racemic cycloalkanones containing an α-alkoxycarbonylmethyl or ethyl group and an α-aryl group. Fortunately, $RuCl_2$[SDP][diamine] complexes efficiently catalyzed the hydrogenation of these substrates, with $RuCl_2[(S_a)$-Xyl-SDP][(*R,R*)-DPEN] (**1d**) leading to the desired product from racemic 2-ethoxycarbonylmethyl-6-phenylcyclohexanone with 98% ee and >99:1 cis,cis selectivity. Interestingly, the ester group in the substrate was hydrogenated to the corresponding alcohol at room temperature during the reaction. Various α-ethoxycarbonylalkyl-α′-arylcycloalkanones were hydrogenated with this catalyst in high yields (86–98%) and with good-to-excellent enantioselectivities (75–99.9% ee) (**eq 5**).[6] Both the side-chain ester group and the aryl group of the substrate were necessary for high enantioselectivity; changing the ester group to an alkyl group led to lower enantioselectivities (Me, 73% ee; Bn, 27% ee). Good-to-high enantioselectivities were also observed when the ester group was replaced with the *N,N*-dimethylaminocarbonyl group ($CONMe_2$, 92% ee), the *N*-benzylaminocarbonyl group (CONHBn, 79% ee), or the benzyloxymethyl group ($BnOCH_2$, 84% ee).

Using this highly efficient method for constructing a cyclic alcohol with three contiguous stereocenters, we synthesized the amaryllidaceae alkaloid (+)-γ-lycorane in 45% overall yield from commercially available 2-cyclohexenone in 8 steps (**Scheme 6**).[6]

Chung et al. recently employed the asymmetric hydrogenation via DKR of racemic 1,2-diaryl-1-pentanone—using $RuCl_2[(S_a)$-Xyl-SEGPHOS®][*S*)-DAIPEN] (Xyl-SEGPHOS® = 5,5′-bis(di-3,5-xylylphosphino)-4,4′-bi-1,3-benzodioxole) as catalyst (0.02 mol %)—

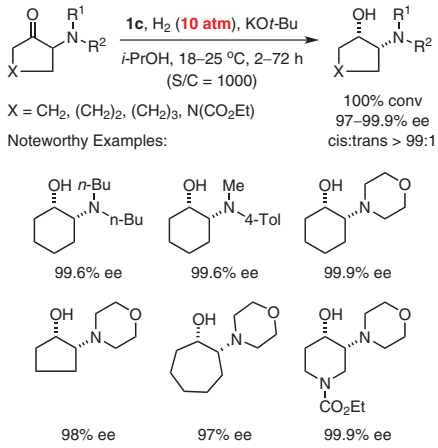
in the synthesis of a glucagon receptor antagonist on a kilogram scale (110 kg) with 98.5% ee and 99% syn-selectivity.[29]

2.3. α-Aminoalkanones to Chiral 1,2-Amino Alcohols

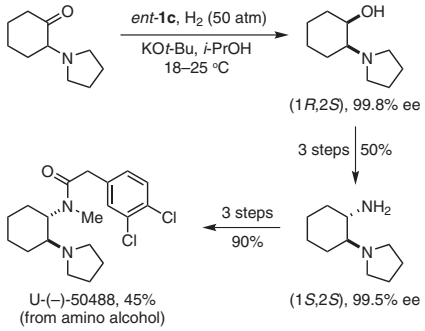
Chiral 1,2-amino alcohols are present in various natural products and are a key functional group in biologically active molecules; optically pure amino alcohols have also been employed as chiral ligands and auxiliaries in asymmetric synthesis.[30] Noyori and co-workers reported in 2000 the first example of the asymmetric hydrogenation via DKR of racemic α-amino ketones, specifically 2-(*tert*-butoxycarbonylamino)-cyclohexanones, to chiral 1,2-amino alcohols with two stereogenic centers; the reaction, however, was only moderately enantioselective (82% ee).[31] In 2007, we reported that $RuCl_2[(S_a)$-SDP][(*R*,*R*)-DPEN] (**1c**) efficiently catalyzed the hydrogenation of racemic *N*,*N*-disubstituted α-aminocycloalkanones to the corresponding chiral *cis*-β-aminocycloalkanols in 97–99.9% ee, >99:1 cis:trans selectivity, and with turnover numbers of up to 30,000 (**eq 6**).[32] The reaction was highly tolerant of substituents on the dialkylamino group with respect to enantioselectivity and diastereoselectivity, whereas the reaction rate was sensitive to the nature of the dialkylamino group. Substrates with benzyl- or aryl-substituted amino groups required longer reaction times or higher hydrogenation pressures for complete reaction. The enantioselectivity of the reaction was slightly lower for substrates with a five- or seven-membered ring. An aza analogue of α-dialkylaminocyclohexanone underwent the hydrogenation reaction with excellent enantioselectivity (99.9% ee) and cis:trans selectivity (>99:1).[32]

An advanced intermediate for the synthesis of U-(−)-50488, a highly selective κ-opioid agonist,[33] was synthesized by this method (**Scheme 7**).[32] Asymmetric hydrogenation of 2-(pyrrolidin-1-yl)-cyclohexanone led to the corresponding (1*R*,2*S*) amino alcohol in 99.8% ee. Mesylation of the hydroxyl group, followed by treatment with NaN_3 and Pd/C-catalyzed hydrogenation led to chiral *trans*-2-(pyrrolidin-1-yl)cyclohexanamine in 99.5% ee. This result suggests that substitution of the mesyl group occurred by a mechanism that did not involve the formation of an aziridinium intermediate,[34] with the cis relationship between the pyrrolidino and mesyl groups being unfavorable for the formation of an aziridinium ion. The chiral *trans*-1,2-diamine was transformed into U-(−)-50488 in 90% yield over three steps.

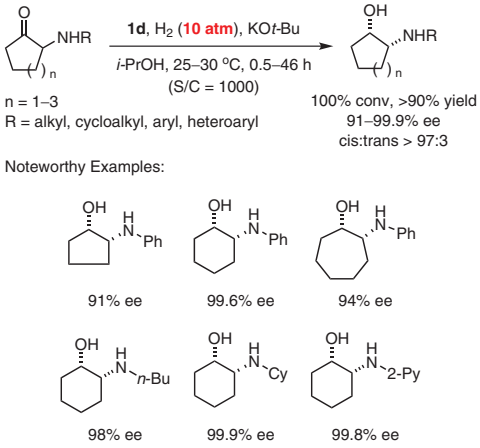
$RuCl_2[(S_a)$-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) was the best catalyst for the asymmetric hydrogenation of racemic α-aminocycloalkanones with a secondary amino group, providing a series of chiral β-*N*-alkylamino- and β-*N*-arylaminocycloalkanols with 91–99.9% ee and >97:3 cis:trans diastereoselectivities (**eq 7**).[35] The enantioselectivity and diastereoselectivity of the reaction were unaffected by the nature of the substituent on the *N*-phenyl ring of the substrate. However, owing to their low solubility in 2-propanol, substrates with a *para*-bromo atom or an *ortho*-methoxy group on the *N*-phenyl ring required longer reaction times to undergo complete hydrogenation. Substrates with an *N*-alkylamino group also underwent the reaction with excellent enantioselectivities (98–99.9% ee) and cis:trans diastereoselectivities (>98:2). α-Aminocyclopentanones and α-aminocycloheptanones were also hydrogenated to the desired chiral *cis*-β-(*N*-arylamino)-cycloalkanols with high enantioselectivities (91% and 94% ee, respectively) and high diastereoselectivities (cis:trans = 98:2 and 99:1, respectively). These results demonstrate that the rigidity and steric bulk of the spiro diphosphine ligand could be preventing coordination of the NH group of the substrates and products with the metal of the catalyst. Such coordination has previously been reported to be the major reason for catalyst deactivation.[36]



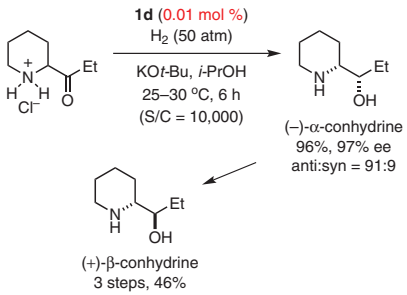
eq 6 *(Ref. 32)*



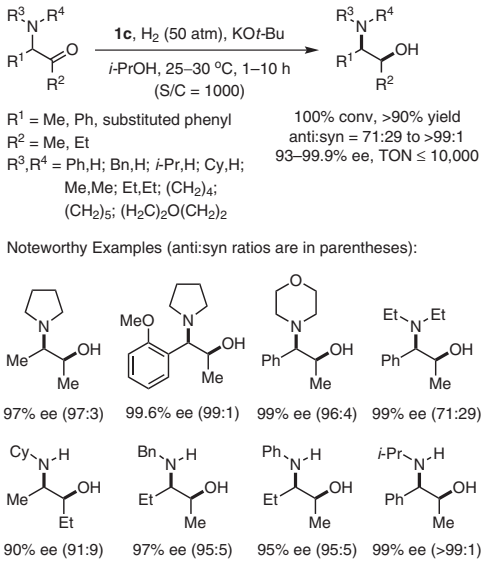
Scheme 7. Enantioselective Synthesis of U-(–)-50488, a Highly Selective κ-Opioid Agonist. *(Ref. 32)*



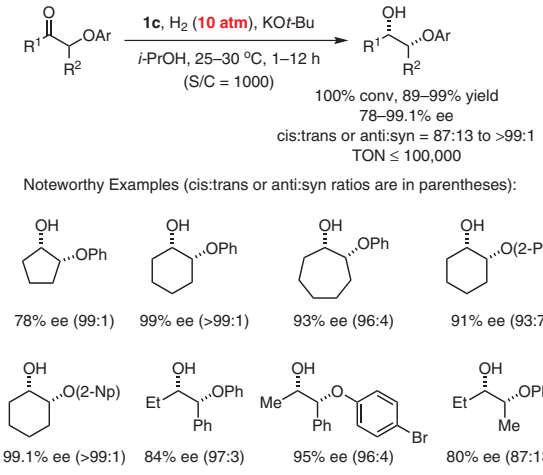
eq 7 *(Ref. 35)*



Scheme 8. Enantioselective Synthesis of the Alkaloids (–)-α- and (+)-β-Conhydrines. *(Ref. 35)*



Scheme 9. Asymmetric Hydrogenation of Racemic, Acyclic α-*N*-Alkylamino- and α-*N*-Arylaminoalkanones. *(Ref. 38)*



eq 8 *(Ref. 43)*

With $RuCl_2[(S_a)$-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) as catalyst, 1-(piperidinyl)-1-propanone was hydrogenated—in 96% yield, 97% ee, and 91:9 anti:syn selectivity at a remarkable catalyst loading of only 0.01 mol % and TON = 10,000—to the chiral amino alcohol *anti*-1-(piperidinyl)-1-propanol,[35] also known as (–)-α-conhydrine, which is an alkaloid isolated from the seeds and leaves of hemlock (*Conium maculatum L.*).[37] Treatment of optically active (–)-α-conhydrine with sulfuryl chloride (SO_2Cl_2) afforded a cyclic sulfate, which underwent ring-opening acetylation with NaOAc; subsequent hydrolysis with K_2CO_3 in MeOH gave (+)-β-conhydrine in 46% overall yield (**Scheme 8**).[35]

Conformationally flexible substrates, such as racemic acyclic a-substituted aliphatic ketones, are more difficult to hydrogenate enantioselectively and diastereoselectively. In an investigation of the asymmetric hydrogenation of conformationally flexible, acyclic aliphatic α-*N*,*N*-dialkylamino ketones, we found that $RuCl_2[(S_a)$-SDP][(*R*,*R*)-DPEN] (**1c**) was an efficient catalyst, affording the corresponding chiral amino alcohols with 93–99.9% ee and 71:29 to >99:1 anti:syn selectivities (**Scheme 9**).[38] The α-dialkylamino group of the substrates strongly influenced the diastereoselectivity of the reaction: Generally, ketones with a small dialkylamino group, such as dimethylamino or pyrrolidino, provided high diastereoselectivities. However, when the bulkier diethylamino group was present, the diastereoselectivity decreased. It is worth noting that the catalyst loading for this hydrogenation reaction could be lowered to 0.01 mol % without an obvious decrease in enantioselectivity or diastereoselectivity. The related α-amino ketones with a secondary amino group afforded the corresponding chiral β-amino alcohols with high enantioselectivities (90-99% ee) and high anti:syn selectivities (91:9 to >99:1) (Scheme 9).[38]

Ohkuma and co-workers reported that $RuCl_2[(S_a)$-Tol-BINAP]-[(*R*)-DMAPEN] (DMAPEN = *N*,*N*′-dimethyl-2-phenylethane-1,2-diamine) catalyzed the hydrogenation of racemic 2-amino-1-phenyl-1-propanone to the corresponding chiral 1,2-amino alcohol, which is an intermediate in the synthesis of the widely used nasal decongestant pseudoephedrine,[39] as well as a useful chiral auxiliary in synthetic organic chemistry.[40] High enantioselectivity and high syn-selectivity were obtained under the optimal reaction conditions. Itsuno and co-workers achieved excellent enantioselectivity and syn-selectivity in the hydrogenation of 2-(*N*-benzoyl-*N*-methylamino)propiophenone by employing polymer-immobilized $RuCl_2[(R_a)$-BINAP][(*S*,*S*)-DPEN], and the catalyst could be recycled five times without any loss in enantioselectivity.[41] Hibino et al. reported that nickel complexes with chiral diphosphine ligands catalyzed the asymmetric hydrogenation of racemic aromatic α-amino ketones, although a high catalyst loading (10 mol %) and high hydrogen pressure (100 atm H_2) were required.[42]

2.4. α-Aryloxyalkanones to β-Aryloxy Alcohols

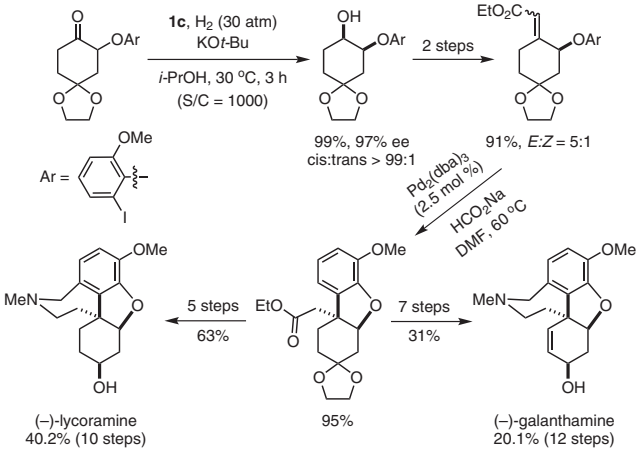
Chiral β-aryloxy alcohols are common structural units in pharmaceuticals and bioactive natural products. We have developed a highly efficient method for the preparation of optically active secondary β-aryloxy alcohols with two adjacent stereocenters that relies on the asymmetric hydrogenation of racemic, aliphatic α-aryloxy ketones via DKR in the presence of $RuCl_2[(S_a)$-SDP][(*R*,*R*)-DPEN] (**1c**) (**eq 8**).[43] Conformationally rigid substrates, such as racemic cyclic α-aryloxy ketones, gave higher enantioselectivities (>91% ee) and higher cis:trans selectivities (>93:7), except for cyclopentanones (78% ee, cis:trans = 99:1). Good-to-high enantioselectivities (80–96% ee) and anti:syn selectivities (87:13 to 98:2) were achieved with conformationally flexible acyclic α-aryloxy ketones. The catalyst

was highly efficient with TONs of up to 100,000. This reaction has been employed to prepare the key intermediate in the synthesis of nonsteroidal glucocorticoid modulators.[44]

The alkaloid (–)-galanthamine,[45] which has been employed in the early treatment of Alzheimer's disease, contains a unique tricyclic tetrahydrodibenzofuran core structure and a chiral arylated quaternary carbon center. Encouraged by our successful synthesis of chiral β-aryloxy alcohols, we developed a new strategy for the total synthesis of (–)-galanthamine by employing the asymmetric hydrogenation of an α-aryloxycyclohexanone as a key step (**Scheme 10**).[46] In the presence of $RuCl_2$[(S_a)-SDP][(*R*,*R*)-DPEN] (**1c**), the hydrogenation yielded the corresponding chiral β-aryloxycyclohexanol in high yield (99%) and with excellent enantioselectivity (97% ee) and cis:trans selectivity (>99:1). The hydrogenation product was converted into (–)-galanthamine in 20% yield over 12 steps, including a Pd-catalyzed intramolecular reductive Heck cyclization to install the chiral arylated quaternary carbon center. Employing the same strategy, (–)-lycoramine,[47] an acetylcholinesterase inhibitor and an allosteric potentiating ligand, was synthesized in 10 steps with a 40% overall yield.[46]

3. Summary and Outlook

Our ongoing search for efficient methods to prepare chiral alcohols for the eventual synthesis of natural products and chiral pharmaceuticals, has led us to investigate the ruthenium-catalyzed asymmetric hydrogenation via DKR of racemic α-substituted alkanones and aldehydes. Racemic α-aryl and α-aryloxy aldehydes; α-aryl, aryloxy, and aminoalkanones; and α,α′-disubstituted alkanones were hydrogenated to the corresponding chiral primary and secondary alcohols with excellent enantioselectivities and diastereoselectivities by employing chiral spiro ruthenium complexes as catalysts. These highly efficient methods were successfully utilized to synthesize chiral pharmaceuticals and natural products. Perhaps most importantly, we have demonstrated that the catalytic asymmetric hydrogenation of racemic α-substituted alkanones and aldehydes via DKR is a promising method for the preparation of diverse chiral alcohols possessing one, two, or even three stereogenic centers. Moreover, we have shown that natural products can inspire the design and development of new reactions, such as the catalytic asymmetric hydrogenation of racemic aldehydes and ketones via DKR. Efficient synthetic methods are still lacking for many bioactive molecules, in particular, complex natural products. We plan to continue to develop highly efficient methods for the synthesis of diverse chiral alcohols with the goal of offering new approaches for the synthesis of pharmaceuticals and natural products.



Scheme 10. Enantioselective Synthesis of (–)-Galanthamine and (–)-Lycoramine. *(Ref. 46)*

4. Acknowledgments

We thank the National Natural Science Foundation of China, the National Basic Research Program of China (973 Program) (2012CB821600), and the "111" project (B06005) of the Ministry of Education of China for financial support.

5. References

(1) (a) Ohkuma, T.; Noyori, R. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; pp 1105–1163. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (c) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563. (d) Pellissier, H. *Tetrahedron* **2011**, *67*, 3769. (e) Xie, J.-H.; Zhou, Q.-L. *Acta Chim. Sinica* **2012**, *70*, 1427. (f) Zhao, B.; Han, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4744.

(2) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872.

(3) Matsumoto, T.; Murayama, T.; Mitsuhashi, S.; Miura, T. *Tetrahedron Lett.* **1999**, *40*, 5043.

(4) (a) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. (b) Xie, J.-H.; Zhou, Q.-L. *Acta Chim. Sinica* **2014**, *72*, 778.

(5) (a) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581. (b) Zhou, Q.-L.; Xie, J.-H. In *Asymmetric Catalysis from a Chinese Perspective*; Topics in Organometallic Chemistry Series, Vol. 36; Ma, S., Ed.; Springer: Berlin Heidelberg, 2011; pp 1–28. (c) Ding, K.; Han, Z.; Wang, Z. *Chem.–Asian J.* **2009**, *4*, 32.

(6) Liu, C.; Xie, J.-H.; Li, Y.-L.; Chen, J.-Q.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 593.

(7) Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1868.

(8) Zhou, Z.-T.; Xie, J.-H.; Zhou, Q.-L. *Adv. Synth. Catal.* **2009**, *351*, 363.

(9) Li, X.; List, B. *Chem. Commun*. **2007**, 1739.

(10) Mihalcik, D. J.; Lin, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 6229.

(11) Brenna, E.; Negri, C. D.; Fuganti, C.; Gatti, F. G.; Serra, S. *Tetrahedron: Asymmetry* **2004**, *15*, 335.

(12) Shan, G.; Stoutamire, D. W.; Wengatz, I.; Gee, S. J.; Hammock, B. D. *J. Agric. Food Chem.***1999**, *47*, 2145.

(13) Hatzelmann, A.; Fruchtmann, R.; Mohrs, K. H.; Raddatz, S.; Müller-Peddinghaus, R. *Biochem. Pharmacol.* **1993**, *45*, 101.

(14) Scalone, M.; Waldmeier, P. *Org. Process Res. Dev.* **2003**, *7*, 418.

(15) Ohkuma, T.; Li, J.; Noyori, R. *Synlett* **2004**, 1383.

(16) Xie, J.-H.; Liu, S.; Huo, X.-H.; Cheng, X.; Duan, H.-F.; Fan, B.-M.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 2967.

(17) Cheng, L.-J.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *Adv. Synth. Catal.* **2012**, *354*, 1105.

(18) Li, G.; Xie, J.-H.; Hou, J.; Zhu, S.-F.; Zhou, Q.-L. *Adv. Synth. Catal.* **2013**, *355*, 1597.

(19) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646.

(20) Cheng, L.-J.; Xie, J.-H.; Chen, Y.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2013**, *15*, 764.

(21) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561.

(22) Chen, C.; Frey, L. F.; Shultz, S.; Wallace, D. J.; Marcantonio, K.; Payack,

J. F.; Vazquez, E.; Springfield, S. A.; Zhou, G.; Liu, P.; Kieczykowski, G. R.; Chen, A. M.; Phenix, B. D.; Singh, U.; Strine, J.; Izzo, B.; Krska, S. W. *Org. Process Res. Dev.* **2007**, *11*, 616.

(23) Lin, L. S.; Lanza, T. J., Jr.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H.; Tong, X.; Wang, J.; Xu, S. S.; Fong, T. M.; Shen, C.-P.; Lao, J.; Xiao, J. C.; Shearman, L. P.; Stribling, D. S.; Rosko, K.; Strack, A.; Marsh, D. J.; Feng, Y.; Kumar, S.; Samuel, K.; Yin, W.; van der Ploeg, L. H. T.; Goulet, M. T.; Hagmann, W. K. *J. Med. Chem*. **2006**, *49*, 7584.

(24) Xie, J.-H.; Kong, W.-L.; Wang, X.-C.; Bai, W.-J.; Wang, L.-X.; Zhou, Q.-L. *Front. Chem. China* **2009**, *4*, 299.

(25) (a) Iwasawa, Y.; Shibata, J.; Nonoshita, K.; Arai, S.; Masaki, H.; Tomimoto, K. *Tetrahedron* **1996**, *52*, 13881. (b) Iwasawa, Y.; Nonoshita, K.; Tomimoto, K. *Tetrahedron Lett*. **1995**, *36*, 7459.

(26) (+)-γ-Lycorane was obtained by Kotera in his degradation studies of lycorine, see Kotera, K. *Tetrahedron* **1961**, *12*, 248.

(27) (a) Prelog, V.; Wiesner, K.; Khorana, H. G.; Kenner, G. W. *Helv. Chim. Acta* **1949**, *32*, 453. (b) Iida, H.; Takarai, T.; Kibayashi, C. *J. Org. Chem.* **1978**, *43*, 975. (c) Zhao, Y.-M.; Gu, P.; Tu, Y.-Q.; Zhang, H.-J.; Zhang, Q.-W.; Fan, C.-A. *J. Org. Chem*. **2010**, *75*, 5289.

(28) (a) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, pp 323–424. (b) Jin, Z. *Nat. Prod. Rep*. **2003**, *20*, 606.

(29) Chung, J. Y. L.; Steinhuebel, D.; Krska, S. W.; Hartner, F. W.; Cai, C.; Rosen, J.; Mancheno, D. E.; Pei, T.; DiMichele, L.; Ball, R. G.; Chen, C.; Tan, L.; Alorati, A. D.; Brewer, S. E.; Scott. J. P. *Org. Process Res. Dev.* **2012**, *16*, 1832.

(30) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.

(31) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510.

(32) Liu, S.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7506.

(33) (a) Masakatsu, T.; Toshihiko, S.; Hiroshi, K. *Eur. J. Pharmacol* **1991**, *200*, 293. (b) Tao, P.-L.; Hwang, C.-L.; Chen, C.-Y. *Eur. J. Pharmacol* **1994**, *256*, 281.

(34) González-Sabín, J.; Gotor, V.; Rebolledo, F. *J. Org. Chem.* **2007**, *72*, 1309.

(35) Liu, S.; Xie, J.-H.; Li, W.; Kong, W.-L.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett*. **2009**, *11*, 4994.

(36) Shang, G.; Liu, D.; Allen, S. E.; Yang, Q.; Zhang, X. *Chem.—Eur. J.* **2007**, *13*, 7780.

(37) Wertheim, T. *Liebigs Ann. Chem.* (presently *Eur. J. Org. Chem.*) **1856**, *100*, 328.

(38) Xie, J.-H.; Liu, S.; Kong, W.-L.; Bai, W.-J.; Wang, X.-C.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 4222.

(39) (a) Arai, N.; Ooka, H.; Azuma, K.; Yabuuchi, T.; Kurono, N.; Inoue, T.; Ohkuma, T. *Org. Lett.* **2007**, *9*, 939. (b) Ooka, H.; Arai, N.; Azuma, K.; Kurono, N.; Ohkuma, T. *J. Org. Chem.* **2008**, *73*, 9084.

(40) (a) Hughes, D. T.; Empey, D. W.; Land, M. *J. Clin. Hosp. Pharm.* **1983**, *8*, 315. (b) Myers, A. G.; Charest, M. G. In *Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., 2003; pp 485–496.

(41) Chiwara, V. I.; Haraguchi, N.; Itsuno, S. *J. Org. Chem.* **2009**, *74*, 1391.

(42) Hibino, T.; Makino, K.; Sugiyama, T.; Hamada, Y. *ChemCatChem* **2009**, *1*, 237.

(43) Bai, W.-J.; Xie, J.-H.; Li, Y.-L.; Liu, S.; Zhou, Q.-L. *Adv. Synth. Catal.* **2010**, *352*, 81.

(44) (a) Berger, M.; Bergström, L.; Dahmén, J.; Eriksson, A.; Gabos, B.; Hemmerling, M.; Henriksson, K.; Ivanova, S.; Lepistoe, M.; McKerrecher, D.; Nilsson, S.; Rehwinkel, H.; Taflin, C. World Patent Appl. WO 2008063116 A1, May 29, 2008. (b) Berger, M.; Dahmén, J.; Eriksson, A.; Gabos, B.; Hansson, T.; Hemmerling, M.; Henriksson, K.; Ivanova, S.; Lepistoe, M.; Mckerrecher, D.; Munck, A. R. M.; Nilsson, S.; Rehwinkel, H.; Taflin, C. World Patent Appl. WO 2008076048 A1, June 26, 2008.

(45) Sramek, J. J.; Frackiewicz, J. E.; Cutler, N. R. *Expert Opin. Investig. Drugs* **2000**, *9*, 2393.

(46) Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett*. **2012**, *14*, 2714.

(47) Han, S. Y.; Sweeney, J. E.; Bachman, E. S.; Schweiger, E. J.; Forloni, G.; Coye, J. T.; Davis, B. M.; Joullié, M. M. *Eur. J. Med. Chem.* **1992**, *27*, 673.

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Jian-Hua Xie was born in 1968. He received his Ph.D. degree in 2003 under the supervision of Professor Qi-Lin Zhou at the Institute of Elemento-organic Chemistry, Nankai University. He then worked in the same institute, and was promoted to Associate Professor in 2005 and to Full Professor in 2010. In 2007, he spent one year as a postdoctoral fellow in Prof. Michael Doyle's group at Maryland University. His research interests focus on asymmetric catalysis and the asymmetric synthesis of natural products and chiral drugs.

Qi-Lin Zhou obtained his Ph.D. degree in 1987 from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. After several years of postdoctoral research (with Professors Klaus Müllen, Andreas Pfaltz, and Michael Doyle), he started his independent research in 1996 at East China University of Science and Technology, Shanghai, China. In 1999, he moved to the Institute of Elemento-Organic Chemistry, Nankai University, as Cheung Kong Scholar. His research interests include organometallics, synthetic methodology, and asymmetric catalysis.

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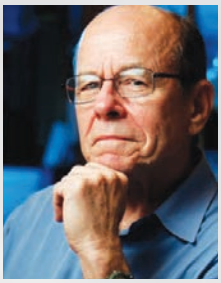
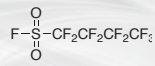


Professor K. Barry Sharpless

Monofunctional



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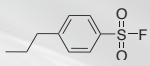

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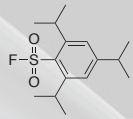

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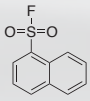

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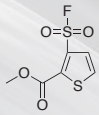

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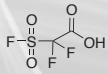

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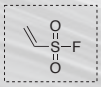

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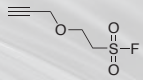

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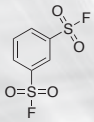

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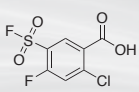

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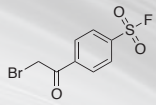

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References:

(1) Dong, J.; Sharpless, K. B.; Kwisnek, L.; Oakdale, J. S.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2014,** *53*, 9466.

(2) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2014,** *53*, 9430.

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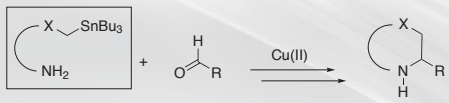
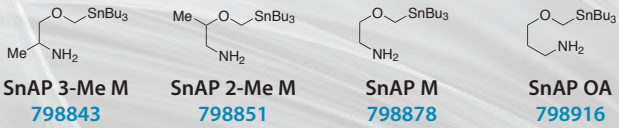
Left to right: Mr. Michael U. Luescher, Dr. Paula L. Nichols, Professor Dr. Jeffrey W. Bode, and Dr. Kimberly Geoghegan



SnAP Reagent | Aldehyde | Saturated N-Heterocycle



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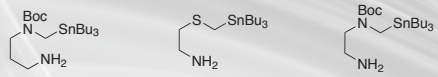
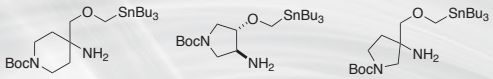
SnAP 2-Me M 798851

SnAP M 798878

SnAP OA 798916



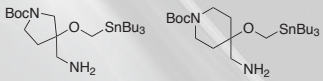
SnAP DA† **SnAP TM**† **SnAP Pip**†



SnAP 3-Spiro-(4-Pip) M†

SnAP 2,3-Bicyclo-(3,4-Pyr) M†

SnAP 3-Spiro-(3-Pyr) M†



SnAP 2-Spiro-(3-Pyr) M†

SnAP 2-Spiro-(4-Pip) M†

† Available soon

References:

(1) Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. *Nat. Chem.* **2014,** *6,* 310.
(2) Siau, W.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2015,** *136,* 17726.
(3) Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. *Org. Lett.* **2014,** *16,* 1236.
(4) Vo, C.-V. T.; Mikutis, G.; Bode, J. W. *Angew. Chem., Int. Ed.* **2013,** *52,* 1705.

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SnAP Reagents for a Cross-Coupling Approach to the One-Step Synthesis of Saturated N-Heterocycles


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Dr. K. Geoghegan


Dr. P. L. Nichols


Prof. Dr. J. W. Bode

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Keywords. SnAP reagents; saturated N-heterocycle synthesis; cross-coupling methodology; medium-size rings.

Abstract. Saturated N-heterocycles can be found with increasing frequency in bioactive molecules, despite their limited commercial availability and challenging synthetic routes. A direct extension of aromatic cross-coupling methods to include saturated N-heterocycles remains elusive. However, the coupling of commercially available, or easily accessible, SnAP reagents with a wide range of aldehydes and ketones offers an alternative, practical, and versatile approach to saturated N-heterocycles.

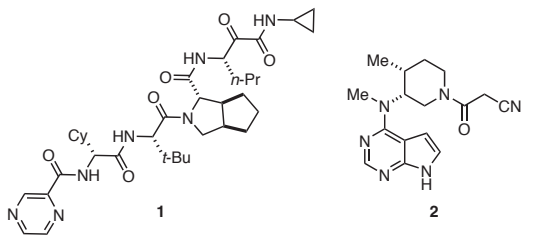
Outline

1. Introduction

Following the extraordinary success of metal-catalyzed cross-coupling reactions in organic chemistry over the last few decades, the number of easily appended aromatic groups in bioactive molecules has increased dramatically. However, a high aromatic-ring count often leads to development-limiting problems associated with poor solubility, pharmacokinetics, and bioavailability.[1] Such issues are now well recognized, and much effort has been directed toward reducing the number of aromatic rings by incorporating alternative groups such as saturated N-heterocycles (**Figure 1**). The incorporation of saturated N-heterocycles introduces solubilizing features, such as ionizable moieties, and a greater diversity of shapes, including chiral elements. It also allows the biological relevance of larger ring systems to be explored, while maintaining a greater degree of control over the overall physicochemical properties of the molecule.

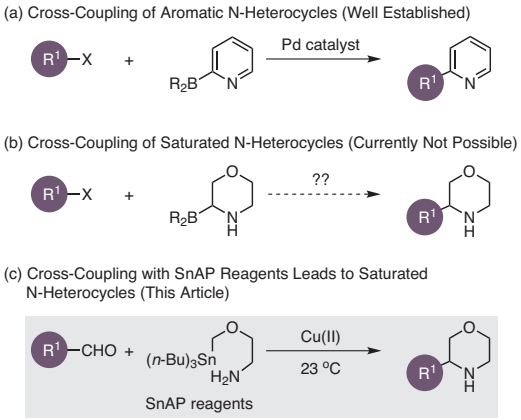
Despite the growing importance of such saturated N-heterocyclic motifs in drug discovery, their installation has been challenging due to poor commercial availability of precursors and the often long and laborious synthetic routes needed to form these ring systems. This stands in contrast to the impressive repertoire of methods for the facile and predictable introduction of N-heteroaromatics, as exemplified by the palladium-catalyzed cross-coupling of stable, and often commercially available, aromatic halides with boronic acids and derivatives (**Scheme 1**, Part (a)).

Unfortunately, a direct extension of the metal-catalyzed cross-coupling to saturated N-heterocycles has been elusive (Scheme 1, Part (b)). Recent efforts to address this well-known limitation have provided promising new methodologies for the derivatization of simple N-heterocycles; but these methods still have considerable shortcomings, including harsh reactions conditions, restricted substrate scope, and intractable N-protecting groups.[2]

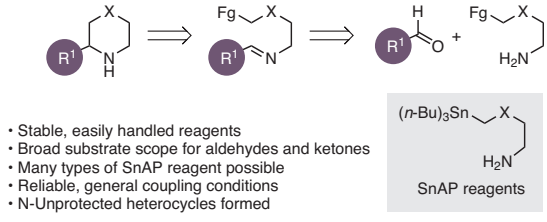


No	Generic Name	Trade Name(s)	FDA Approval	For Treating
1	Telaprevir	Incivek®, Incivo®	2011	Hepatitis C
2	Tofacitinib	Xeljanz®	2012	Rheumatoid arthritis
3	Alogliptin	Nesina®	2013	Type 2 diabetes
4	Suvorexant	Belsomra®	2014	Insomnia

Figure 1. Bioactive Molecules Incorporating Saturated N-Heterocycles.



Scheme 1. Employing the Metal-Catalyzed Cross-Coupling Reaction in the Formation of Saturated N-Heterocycles.



Scheme 2. Genesis of the SnAP Reagent Concept. *(Ref. 3)*

As an alternative to traditional cross-coupling approaches, our group has recently introduced "**SnAP**" [**Sn (tin) Amine Protocol**] as a versatile, predictable methodology for the synthesis of saturated N-heterocycles from widely available aromatic, heteroaromatic, aliphatic, and glyoxylic aldehydes (Scheme 1, Part (c).[3–7] This review will highlight how, since the first report on SnAP reagents in 2013,[3] an increasing number of readily accessible reagents are now available for the convenient synthesis of medium-ring (six- to nine-membered) saturated N-heterocycles. Many of the SnAP reagents are now commercially available, and custom-made reagents for specific applications or targets can be prepared from simple starting materials.

2. SnAP Reagents for N-Heterocycle Synthesis

2.1. Development of SnAP Reagents

Our development of SnAP reagents for the synthesis of N-heterocycles relied on our recognition that an aldehyde could serve as a readily introduced and identified functional group for cross-coupling and as the source of one of the carbon atoms in the ring (**Scheme 2**).[3] This approach would allow coupling of the two starting materials to take place via imine formation—a generally facile and chemoselective process—which is followed by intramolecular cyclization. After considerable experimentation, we identified tin-based reagents as ideal reaction partners in terms of ease of use, substrate scope, and the preparation and stability of the reagents.

Following our first report on SnAP reagents for the preparation of thiomorpholines,[3] we have extended the line of SnAP reagents to include ones suitable for the synthesis of morpholines and piperazines,[4a] a variety of bi- and spirocycles,[5,6] and other medium-size rings.[7] These reagents are easy-to-handle, air- and moisture-stable liquids, and can be synthesized on a multigram scale by employing a straightforward synthetic sequence (**Figure 2**).

Widely available aliphatic, aromatic, and heteroaromatic aldehydes and cyclic ketones are converted into various N-heterocycles using an operationally simple and general reaction protocol (**eq 1**). This process has outstanding substrate scope and functional-group tolerance, and displays an easily recognizable retrosynthetic disconnection. It offers the unprecedented advantage of delivering N-unprotected products directly, which obviates the need to cleave the often difficult-to-remove aryl or benzylic protecting groups that are utilized in traditional C–H functionalization approaches to substituted N-heterocycles.

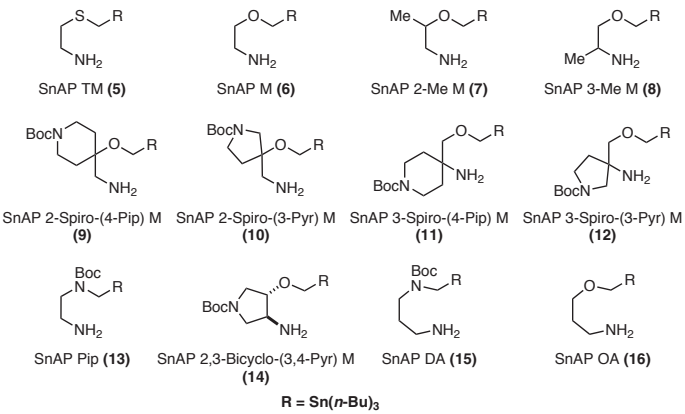


Figure 2. Commercially Available SnAP Reagents for the Synthesis of Unprotected, Saturated N-Heterocycles from Aldehydes and Ketones. *(Ref. 3–7)*

2.2. Synthesis of SnAP Reagents

The easily handled, air- and moisture-stable SnAP reagents can be stored neat at –10 °C for months without notable decomposition. They can be prepared on a multigram scale from inexpensive starting materials by straightforward and efficient routes. Tributyl(iodomethyl)-stannane [$(n\text{-Bu})_3SnCH_2I$; can be stored neat at –10 °C for 1–2 weeks, but decomposes slowly at room temperature] is commercially available or can be synthesized from cheap starting materials in 50–100 g batches in two steps, with only one purification needed.[4a,7]

2.2.1. Morpholine and Thiomorpholine SnAP Reagents and Analogues

Morpholines and thiomorpholines are prepared from amino alcohols and amino thiols, respectively.[3,4a] In general, all amino thiols and amino alcohols with a substituent in the α position to the nitrogen are S- or O-alkylated with tributyl(iodomethyl)stannane in a simple, one-step reaction to afford the desired SnAP reagents.

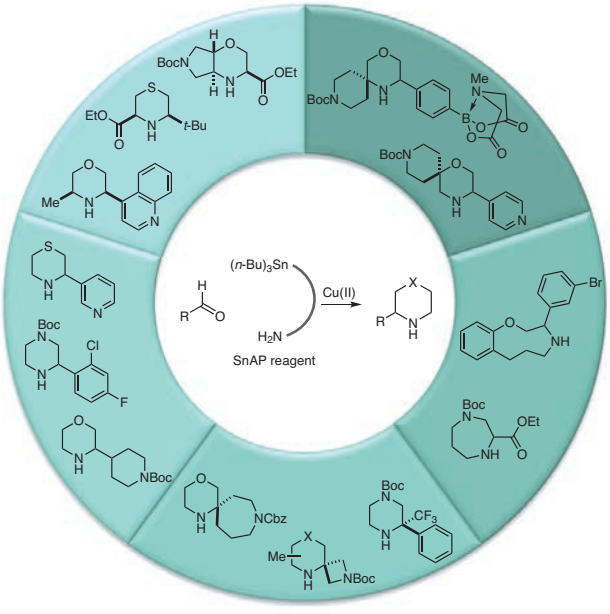
SnAP reagents for morpholines and their medium-size analogues without a substituent in the α position to the amine functionality, or no substituents at all in the backbone, are synthesized in a three-step, two-pot procedure involving protection, O-alkylation, and deprotection steps (**Scheme 3**).[4a,7]

2.2.2. Piperazine SnAP Reagents and Analogues

Piperazine SnAP reagents and their medium-size-ring analogues are synthesized starting either from the amino alcohols or the diamines, depending on the desired substitution pattern on the backbone of the requisite SnAP reagent (**Scheme 4**).[4a,7]

3. Applications of SnAP Reagents

SnAP reagents can be utilized in a simple and effective protocol to prepare a diverse range of saturated, substituted N-heterocycles as exemplified in **Scheme 5**.[4]



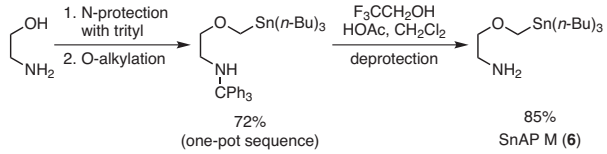
Unprotected, Saturated N-Heterocycles from Aldehydes and Ketones through the Use of Commercially Available SnAP Reagents

eq 1 *(Ref. 3–7)*

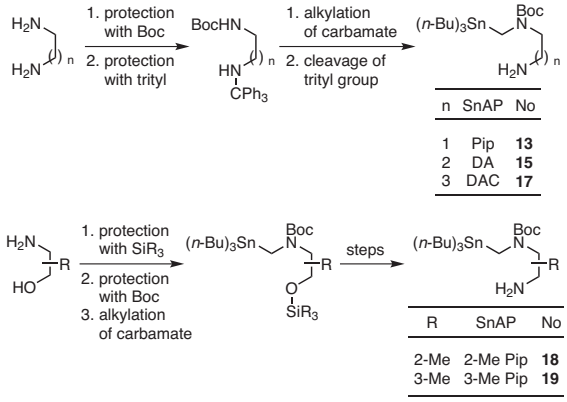
3.1. Synthesis of Six-Membered Rings

Unprotected, substituted morpholines, piperazines, and thiomorpholines prepared with SnAP reagents **5**–**8**, **13**, **18**, **19**, and **20** were obtained in good-to-excellent yields by employing electronically and sterically diverse aromatic, heteroaromatic, and aliphatic aldehydes—one of the most widely available classes of starting material (**eq 2**).[3,4a] A single reaction protocol was employed in all of the cyclization reactions, and we anticipate that substrate-specific optimization should be possible if higher yields and/or faster reaction times are necessary.

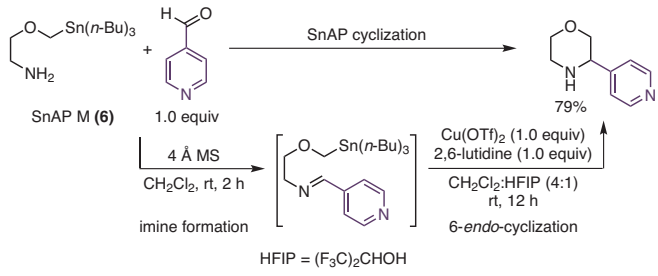
In general, the formation of six-membered rings tolerates a variety of functional groups such as esters, organohalides, amines, and a variety of heterocycles; and the cyclization step takes place under mild conditions at room temperature. For the most challenging substrates, larger amounts of protodestannylated side-products were observed.



Scheme 3. Example of the Preparation of SnAP Reagents Lacking a Substituent α to the Amine Group. *(Ref. 4a)*



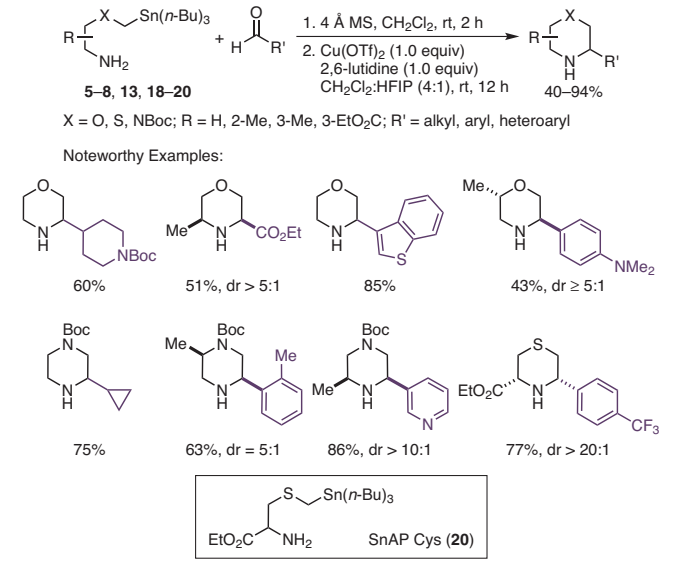
Scheme 4. Synthesis of Piperazine SnAP Reagents and Analogues. *(Ref. 4a,7)*



Scheme 5. Example of the Application of SnAP Reagents in N-Heterocycle Synthesis. *(Ref. 4a)*

3.2. Synthesis of Medium-Size Rings

SnAP reagents can also be utilized to prepare more challenging medium-size rings.[7] Reagents suitable for the synthesis of saturated seven-, eight-, and nine-membered-ring N-heterocycles, including diazepanes and oxazepanes, have been designed and synthesized. The substrate scope and functional group tolerance were similar to those observed in the synthesis of the six-membered-ring analogues, albeit with somewhat lower yields due to increased protodestannylation. It is remarkable, however, that this process can easily access medium-size rings, even in cases where the SnAP reagents do not contain any backbone elements that would favor cyclization (**Figure 3**).[7]



eq 2 *(Ref. 3,4a)*

3.3. Spirocycles from Ketones

Saturated, spirocyclic N-heterocycles[8] are regarded as promising scaffolds for drug discovery and development.[9] However, relatively few multifunctional saturated spirocycles are actually available for use due to the scarcity of methods for their synthesis. A major challenge in this area is the preparation of diverse spirocycles by the union of two discrete components.[10,11] The reaction of cyclic and α-CF_3-substituted ketones with SnAP reagents **6–8**, **13**, **18**, and **19** affords saturated, spirocyclic and α-CF_3-substituted N-heterocycles under operationally simple reaction conditions (**Scheme 6**).[6]

3.4. Customized SnAP Reagents for C-Substituted Spirocycle Formation

We envisaged the preparation of customized SnAP reagents as cross-coupling partners for aldehydes and ketones in order to form more elaborate C-substituted bicyclic and spirocyclic structures. These new SnAP reagents proved compatible with a variety of aldehydes and ketones. The cyclization using our standard SnAP conditions provided the desired C-substituted bicyclic and spirocyclic morpholines and piperazines. Coupling partners containing functional groups such as esters, aldehydes, and a MIDA ester provided scaffolds suitable for further functionalization (**Figure 4**).[5]

3.5. SnAP Reaction Limitations

The main drawback of this methodology is the dependence on tin and its related toxicity.[12] However, the large difference in polarity between the tin byproducts and the desired N-heterocycles simplifies the purification by column chromatography, and most of the tin byproducts

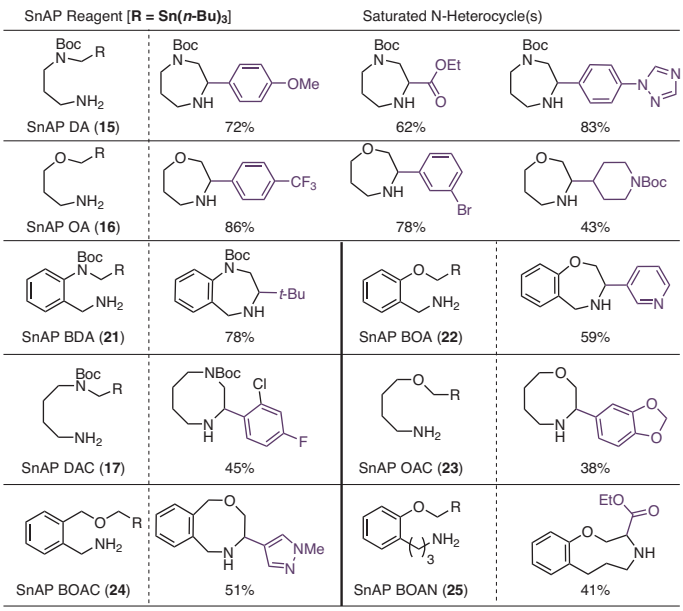
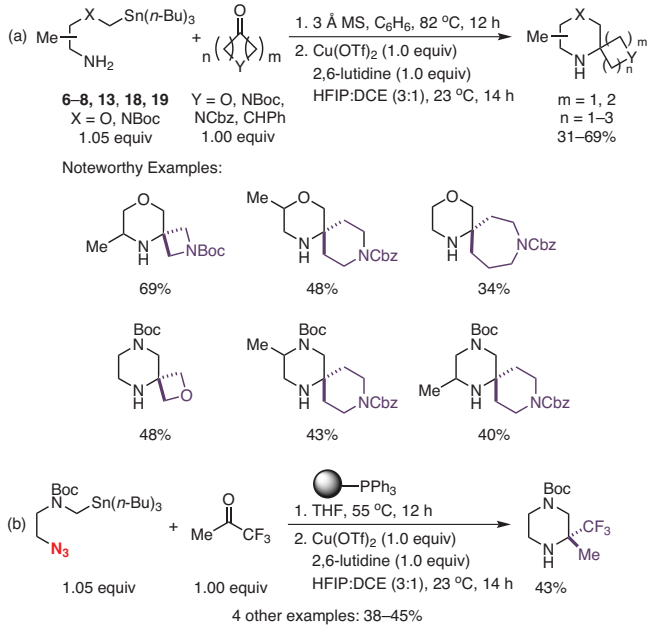


Figure 3. SnAP Reagents and Substrate Scope for Saturated, Medium-Size N-Heterocycles. *(Ref. 7)*



Scheme 6. Synthesis from SnAP Reagents and Ketones of (a) Saturated, Spirocyclic N-Heterocycles and (b) α-Trifluoromethyl N-Heterocycles. *(Ref. 6)*

can be removed prior to purification by simple extraction with mixtures of acetonitrile and hexanes.[13] Furthermore, the unprotected N-heterocycles can be converted into their salts to remove any last traces of tin impurities. The use of aliphatic aldehydes and ketones involves intermediate imines that readily undergo enamine tautomerization; for example, 3-pyrrolidinone and 3-piperidinone. In these cases, along with the desired N-heterocycles, larger amounts of protodestannylation byproducts are typically observed. Efforts toward improving the utility of this class of substrates are currently ongoing.

3.6. Mechanistic Considerations

Our investigation to date implicates a radical-based process initiated by a copper-mediated oxidation of the carbon–tin bond to form a stabilized primary carbon radical (**Scheme 7**).[3,7] Although radical cyclizations onto alkenyls typically proceed via exo-bond formation, the SnAP reagents, as aza analogues, prefer formation of the endo products due to thermodynamic and kinetic factors.[14] In principle, the cyclization should be catalytic in copper, but coordination of the unprotected N-heterocycles to Cu(II) might lead to catalyst inhibition. Efforts to render this process catalytic are yielding encouraging results.

3.7. Catalytic Variant

Preliminary results from the elaborate screening of the reaction conditions—including solvent, ligands, and additives—appear promising. In the presence of a commercially available bisoxazoline ligand and using hexafluoroisopropanol (HFIP) as the sole solvent, the amount of $Cu(OTf)_2$ needed can be lowered to 10 mol %, and the reaction still affords the desired unprotected N-heterocycles with a broad substrate scope (**eq 3**).[15]

4. Conclusion

SnAP reagents are a stable, easy-to-handle, and rapidly expanding class of reagents that offer a convenient and general approach to the synthesis of small-to-medium-size N-heterocycles, bicycles, and spirocycles. They have an outstanding substrate scope, and their coupling with widely available aliphatic, aromatic, and heteroaromatic aldehydes and ketones provides access to a large variety of N-heterocycles that are challenging to prepare using existing synthetic methods. SnAP reagents and their products should be of great interest in drug discovery, since they can provide ready access to differentially substituted analogues for structure–activity relationship (SAR) studies, and since they greatly expand the availability of saturated N-heterocycles.[16,17]

5. References and Notes

(1) Meanwell, N. A. *Chem. Res. Toxicol*. **2011**, *24*, 1420.

(2) (a) Vo, C.-V. T.; Bode, J. W. *J. Org. Chem*. **2014**, *79*, 2809, and references therein. (b) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2012**, *18*, 10092.

(3) Vo, C.-V. T.; Mikutis, G.; Bode, J. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1705.

(4) (a) Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1236. (b) The SnAP reagent and the aldehyde are stirred in CH_2Cl_2 in the presence of molecular sieves to afford the corresponding imine. The solution containing the imine intermediate is filtered through a sintered-glass funnel and evaporated to ensure clean and full conversion before being subjected to the cyclization conditions. Separately, a solution of $Cu(OTf)_2$ and 2,6-lutidine in HFIP (hexafluoroisopropanol) is stirred at rt for one hour, during which a heterogeneous suspension is formed. The solution of the imine in CH_2Cl_2 is added in one portion to this suspension, and the resulting reaction mixture is stirred at rt for 12 hours. Alternatively,

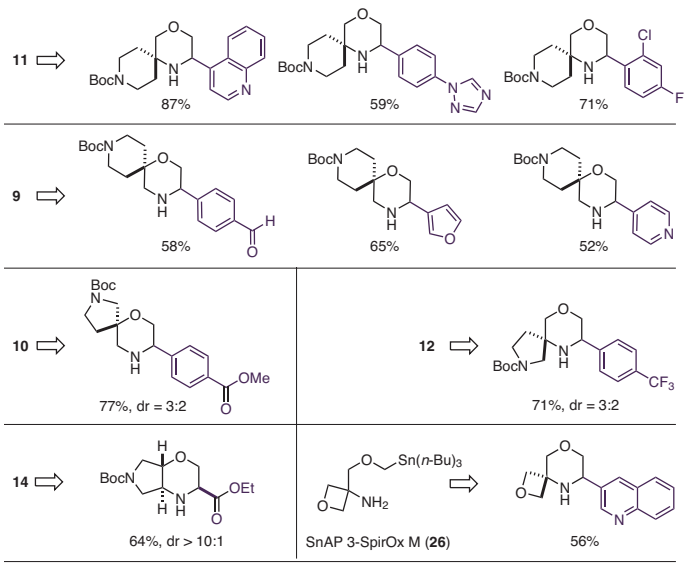
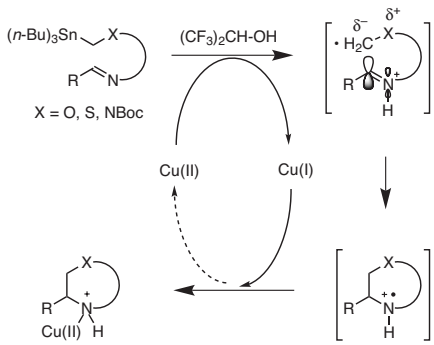
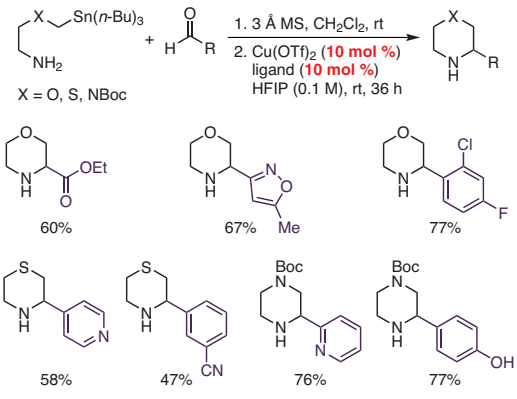


Figure 4. Synthesis of C-Substituted Bicyclic and Spirocyclic Morpholines by Employing Customized SnAP Reagents. *(Ref. 5)*



Scheme 7. Proposed Mechanism for the Second Step of the Reaction of SnAP Reagents with Carbonyl Compounds. *(Ref. 3,7)*



eq 3 *(Ref. 15)*

the imine can be diluted with additional CH_2Cl_2 and transferred to the heterogeneous suspension using a filter-syringe to remove the molecular sieves. Stirring at room temperature for 2–15 h, followed by aqueous workup and purification, affords the desired N-heterocyclic compound.

(5) Geoghegan, K.; Bode, J. W. *Org. Lett.* **2015**, *17*, 1934.

(6) Siau, W.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2014**, *136*, 17726.

(7) Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. *Nat. Chem.* **2014**, *6*, 310.

(8) For a recent review of spirocyclic N-heterocycles, see Carreira, E. M.; Fessard, T. C. *Chem. Rev*. **2014**, *114*, 8257.

(9) For selected examples of the use of spirocyclic scaffolds in drug discovery, see: (a) Link, J. O.; Taylor, J. G.; Xu, L.; Mitchell, M.; Guo, H.; Liu, H.; Kato, D.; Kirschberg, T.; Sun, J.; Squires, N.; Parrish, J.; Keller, T.; Yang, Z.-Y.; Yang, C.; Matles, M.; Wang, Y.; Wang, K.; Cheng, G.; Tian, Y.; Mogalian, E.; Mondou, E.; Cornpropst, M.; Perry, J.; Desai, M. C. *J. Med. Chem*. **2014**, *57*, 2033. (b) Brown, D. G.; Bernstein, P. R.; Griffin, A.; Wesolowski, S.; Labrecque, D.; Tremblay, M. C.; Sylvester, M.; Mauger, R.; Edwards, P. D.; Throner, S. R.; Folmer, J. J.; Cacciola, J.; Scott, C.; Lazor, L. A.; Pourashraf, M.; Santhakumar, V.; Potts, W. M.; Sydserff, S.; Giguère, P.; Lévesque, C.; Dasser, M.; Groblewski, T. *J. Med. Chem.* **2014**, *57*, 733. (c) Bondada, L.; Rondla, R.; Pradere, U.; Liu, P.; Li, C.; Bobeck, D.; McBrayer, T.; Tharnish, P.; Courcambeck, J.; Halfon, P.; Whitaker, T.; Amblard, F.; Coats, S. J.; Schinazi, R. F. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 6325. (d) Efremov, I. V.; Vajdos, F. F.; Borzilleri, K. A.; Capetta, S.; Chen, H.; Dorff, P. H.; Dutra, J. K.; Goldstein, S. W.; Mansour, M.; McColl, A.; Noell, S.; Oborski, C. E.; O'Connell, T. N.; O'Sullivan, T. J.; Pandit, J.; Wang, H.; Wei, B.; Withka, J. M. *J. Med. Chem*. **2012**, *55*, 9069. (e) Griffith, D. A.; Dow, R. L.; Huard, K.; Edmonds, D. J.; Bagley, S. W.; Polivkova, J.; Zeng, D.; Garcia-Irizarry, C. N.; Southers, J. A.; Esler, W.; Amor, P.; Loomis, K.; McPherson, K.; Bahnck, K. B.; Préville, C.; Banks, T.; Moore, D. E.; Mathiowetz, A. M.; Menhaji-Klotz, E.; Smith, A. C.; Doran, S. D.; Beebe, D. A.; Dunn, M. F. *J. Med. Chem*. **2013**, *56*, 7110. (f) Deng, Y.; Yang, Z.; Shipps, G. W., Jr.; Lo, S.-M.; West, R.; Hwa, J.; Zheng, S.; Farley, C.; Lachowicz, J.; van Heek, M.; Bass, A. S.; Sinha, D. P.; Mahon, C. R.; Cartwright, M. E. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 791. (g) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673.

(10) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165.

(11) For examples of two-component cross-coupling reactions that afford spirocyclic compounds, see: (a) Barroso, R.; Valencia, R. A.; Cabal, M.-P.; Valdés, C. *Org. Lett.* **2014**, *16*, 2264. (b) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett.* **2005**, *7*, 4345.

(12) (a) Stoner, H. B.; Barnes, J. M.; Duff, J. I. *Br. J. Pharmacol.* **1955**, *10*, 16. (b) Boyer, I. J. *Toxicology* **1989**, *55*, 253. (c) Snoeij, N. J.; Penninks, A. H.; Seinen, W. *Environ. Res.* **1987**, *44*, 335. (d) Fent, K. *Crit. Rev. Toxicol.* **1996**, *26*, 3.

(13) Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.

(14) (a) Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123. (b) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. (c) Tomaszewski, M. J.; Warkentin, J.; Werstiuk, N. H. *Aust. J. Chem.* **1995**, *48*, 291. (d) Friestad, G. K. *Tetrahedron* **2001**, 57, 5461.

(15) Luescher, M. U.; Bode, J. W. ETH-Zürich, Zürich, Switzerland. Unpublished work, 2015.

(16) Leeson, P. D.; St-Gallay, S. A.; Wenlock, M. C. *Med. Chem. Commun.* **2011**, *2*, 91.

(17) (a) James, T.; MacLellan, P.; Burslem, G. M.; Simpson, I.; Grant, J. A.; Warriner, S.; Sridharan, V.; Nelson, A. *Org. Biomol. Chem.* **2014**, *12*, 2584. (b) Kumar, S.; Thornton, P. D.; Painter, T. O.; Jain, P.; Downard, J.; Douglas, J. T.; Santini, C. *J. Org. Chem.* **2013**, *78*, 6529.

About the Authors

Michael U. Luescher was born in 1985 in Solothurn (Switzerland), and was trained as a laboratory technician in medicinal chemistry at Novartis Pharma AG in Basel (Switzerland). He then earned a B.Sc. degree in chemistry in 2010 from the University of Basel, and joined Professor Dr. Karl Gademann's group for his M.Sc. studies. He started his Ph.D. work in 2012 in Professor Dr. Jeffrey W. Bode's group at ETH-Zürich, where he is currently investigating catalytic protocols using the SnAP methodology.

Kimberly Geoghegan graduated in 2009 with a B.Sc. (Hons) degree in chemistry from University College, Dublin (UCD). She continued her studies at UCD and joined the research group of Dr. Paul Evans. She was awarded a National University of Ireland (NUI) Travelling Studentship to undertake doctoral studies on the regioselective Heck reaction and its applications in the synthesis of natural products, and earned her Ph.D. degree in 2013. Since 2014, Kimberly has been a postdoctoral researcher in the group of Professor Dr. Jeffrey W. Bode at ETH-Zürich, where she is developing a new class of reagents for the synthesis of spirocyclic and bicyclic scaffolds for drug discovery.

Paula L. Nichols undertook her undergraduate studies—which included a year at AstraZeneca, Alderley Park (U.K.)—at the University of Manchester's Institute of Science and Technology. She received her M.Chem. degree in 2000. After earning her Ph.D. degree in 2003 in the group of Professor Nigel Simpkins at the University of Nottingham, she joined GlaxoSmithKline (GSK) as a medicinal chemist. She spent her time at GSK working on numerous projects in the neuroscience, gastrointestinal, and pain therapy areas before moving to Eisai in 2010. Following a move to Switzerland, she joined the group of Professor Dr. Jeffrey W. Bode at ETH-Zürich, where she is currently supporting industrial collaborations.

Jeffrey W. Bode studied at Trinity University in San Antonio, TX (U.S.A.). Following doctoral studies at the California Institute of Technology and ETH-Zürich, and postdoctoral research at the Tokyo Institute of Technology (Japan), he began his independent academic career at UC Santa Barbara in 2003. In 2007, he accepted an appointment as Associate Professor at the University of Pennsylvania, and, in 2010, as Full Professor at ETH-Zürich. He has also been Principal Investigator and Visiting Professor at the Institute of Transformative Biomolecules (WPI-ITbM) at Nagoya University (Japan) since 2013.

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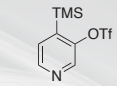

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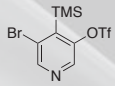

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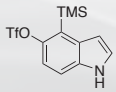

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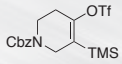

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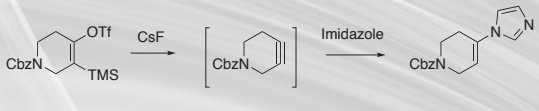

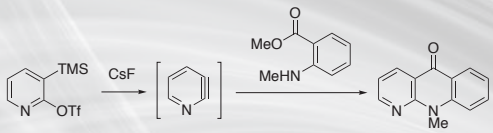

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(1) Im, G-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010,** *132,* 17933.
(2) Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013,** *5,* 54.
(3) Saito, N.; Nakamura, K.; Shibano, S.; Ide, S.; Minami, M.; Sato, Y. *Org. Lett.* **2013,** *15,* 386.
(4) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2014,** *136,* 15798.
(5) Goetz, A. E.; Shah, T. K.; Garg, N. K. *Chem. Commun.* **2015,** *51,* 34.
(6) McMahon, T. C.; Medina, J. M.; Yang, Y.-F.; Simmons, B. J.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2015,** *137,* 4082.

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Prod. No.	Solvent Alternatives	Undesired Solvents	Applications
745588	Ethyl acetate/Ethanol 3:1 (v/v) solution, CHROMASOLV®	DCM	Purification, Analysis[1,2]
34873	Heptane, CHROMASOLV®, for HPLC, ≥99%	Hexane, pentane	Reaction, Analysis[3]
246654	Heptane, anhydrous, 99%	Hexane, pentane	Reaction, Purification[3]
673277	2-Methyltetrahydrofuran, anhydrous, ≥99%, inhibitor-free (2-MeTHF)	DCM, THF, diisopropyl ether, diethyl ether	Reaction[4]
414247	2-Methyltetrahydrofuran, anhydrous, ≥99.0%, contains 250 ppm BHT as stabilizer (2-MeTHF)	DCM, THF	Reaction[4]
791962	Cyclopentyl methyl ether, anhydrous, ≥99.9%, inhibitor-free (CPME)	THF, MTBE, 1,4-dioxane and other ether solvents	Reaction,[5] Purification[6]
675970	Cyclopentyl methyl ether, anhydrous, ≥99.9%, contains 50 ppm BHT as inhibitor (CPME)	THF, MTBE, 1,4-dioxane and other ether solvents	Reaction,[5] Purification[6]
270989	Ethyl acetate, anhydrous, 99.8%	DCM, DCE	Reaction, Purification[7]
517127	Dimethyl carbonate, anhydrous, ≥99% (DMC)	DMF, DCM, DME	Reaction[8]
244511	Toluene, anhydrous, 99.8%	Benzene	Reaction[7]
271004	Acetonitrile, anhydrous, 99.8%	DMF, DMA, NMP	Reaction[7]

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References:

(1) A convenient guide to help select replacement solvents for dichloromethane in chromatography. Taygerly, J. P. et al. *Green Chem.* **2012**, *14*, 3020.
(2) Sustainable Practices in Medicinal Chemistry: Current State and Future Directions. Bryan, M. C. et al. *J. Med. Chem.* **2013**, *56*, 6007.
(3) Heptane as a less toxic option than hexane for the separation of vitamin E from food products using normal phase HPLC. Buddrick, O. et al. *RSC Advances* **2013**, *3*, 24063.
(4) 2-Methyltetrahydrofuran (2-MeTHF): A Biomass-Derived Solvent with Broad Application in Organic Chemistry. Pace, V. et al. *ChemSusChem* **2012**, *5*, 1369.
(5) The toxicological assessment of cyclopentyl methyl ether (CPME) as a green solvent. Watanabe, K. *Molecules* **2013**, *18*, 3183.
(6) Replacement of dichloromethane within chromatographic purification: a guide to alternative solvents. MacMillan, D. S. et al. *Green Chem.* **2012**, *14*, 3016.
(7) Expanding GSK's solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry. Henderson, R. K. et al. *Green Chem.* **2011**, *13*, 854.
(8) Evaluation of alternative solvents in common amide coupling reactions: replacement of dichloromethane and *N,N*-dimethylformamide, MacMillan, D. S. et al. *Green Chem.* **2013**, *15*, 596.

Development of Solvent Selection Guides


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Keywords. environment; green chemistry; sustainability; solvents; selection guides.

Abstract. A review of the development of solvent selection guides that focuses on the efforts of major pharmaceutical companies and several academic groups to provide guides that facilitate the selection of more benign solvents for use in synthetic chemistry.

Outline

1. Introduction

The sustainability of chemical processes is of increasing importance within the chemical industry and is becoming a key concern for a wider range of practitioners.[1] Historically, process chemists have been the leading proponents of sustainable chemistry practices and, while this does remain integral to chemical development operations, sustainability is now becoming a significant consideration earlier on in the discovery phase of industrial, as well as academic, research.[2]

In this regard, solvent is one of the largest overall components used in chemical reactions. For example, solvent has been estimated to account for over half of the total material utilized to manufacture active pharmaceutical ingredients.[3] Based on this knowledge, and perhaps unsurprisingly, solvent was identified very early on in the sustainable chemistry revolution as a priority area for research because of the direct and substantial impact that a change in this area may have.

Consequently, over approximately the past 15 years, efforts have been made to identify existing solvents that exhibit undesirable properties from an environment, health, and safety (EHS) perspective such that, wherever possible, solvents with an unacceptable profile may be avoided. In addition, considerable research has been invested in identifying replacements for solvents that are less favorable from a sustainability perspective. These efforts have resulted in a series of solvent selection guides that helpfully describe the alignment of a broad range of widely used solvents with sustainable chemistry principles.

2. Development of Solvent Selection Guides

Two principal approaches have been taken toward providing guidelines to assist with solvent selection. The first helps the practitioner select a priori a more sustainable solvent for a reaction, while the second approach allows an existing less favorable solvent to be supplanted with a more benign alternative. A series of reports have emerged over the past 15 years from leading pharmaceutical companies detailing their assessment of what solvents they consider to be favorable or unfavorable (and anywhere in between). Their evaluations were based on a range of criteria encompassing EHS considerations and considerations that relate to operational costs and impact on life-cycle management.[4–8] In a more applied approach, several industrial and academic groups have published task-specific guides to help facilitate the replacement of an unfavorable solvent within widely used processes or reactions such as chromatographic purification,[9,10] amide-bond formation,[11] reductive amination,[12] and olefin metathesis.[13]

2.1. General Solvent Selection Guides

As stated above, the development of solvent selection guides has been driven principally by industry, in particular, by several large pharmaceutical companies.[4–8] Accordingly, the guidance delivered is broadly similar, with typically only small variations in the perceived environmental impact of a particular solvent, and these variations are generally related to the nature and number of the variables being

employed in the assessment. The use of a traffic-light-type guide to facilitate solvent selection is also common. This familiar representation is broadly accessible for practitioners and is designed to facilitate movement to a more sustainable solvent choice. Over the years, the depth of analysis relating to the sustainability credentials of a given solvent has increased markedly and in parallel with the best guidance available at the time (**Table 1**). In 1999, GlaxoSmithKline (GSK) published the first solvent selection guide,[5a] which has been subsequently embellished with follow-up publications in 2005[5b] and 2011.[5c] In 1999, the level of scrutiny a solvent was subjected to was four-fold: waste, environmental impact, health, and safety. Life-Cycle Analysis (LCA)[14] was included in the analysis by 2005, and a further series of considerations in 2011. The most recent guide, from Sanofi in 2013,[7] employed an extensive range of factors in the analysis, with at least 11 components constituting this new analysis.

Table 1. Development of Solvent Selection Guides by Pharmaceutical Companies: Chronological Escalation of Analysis Detail

Year	Company	Factors Considered in Determining the Sustainability Credentials of a Given Solvent
1999	GlaxoSmithKline	Waste, environmental impact, health, safety
2005	GlaxoSmithKline	Waste, environmental impact, health, safety, LCA
2008	Pfizer	Environmental/regulatory considerations, worker safety
2011	GlaxoSmithKline	Waste, environmental impact, health, safety, LCA, flammability/explosion, reactivity/stability, legislation flag, physical properties
2013	Sanofi	Environmental hazard bands, health, safety, physical properties, water miscibility, source, industrial/legal constraints, ICH limits, biodegradability, resistivity, cost

LCA = life-cycle analysis. ICH = International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use).

The desire to transition away from harmful solvents to more favorable alternatives on an industrial scale was clearly demonstrated by GSK in an analysis of its pilot plant operations.[3] For example, undesirable dichloromethane ranked #3 for usage in 1999, but dropped to #8 in 2005, a positive movement away from the use of this solvent. Conversely, the more favorable isopropyl alcohol increased in usage from #5 to #1 in the same period of time, while heptane (a hexane replacement) increased from #12 to #5, again demonstrating positive movements toward solvents that, following the available guidance, were considered more benign.

The perspective of precisely how well aligned a particular solvent is with the ethos of sustainability has closely correlated with the available guidance, and this perspective has evolved as the guidance has developed and matured. An analysis of the evolution of GSK's solvent guide over 12 years (through the three published iterations) provides an interesting snapshot of how perspectives changed as a function of time (**Figure 1**).[5] For example, taking a subset of 12 common solvents and tracking the average sustainability score (as a percentage of the total possible score) arising from GSK's analysis using selected available variables from 1999 (4), 2005 (5), and 2011 (6) illustrate the change in perceived sustainability over this time period (note that legislation issues are not taken into account). In particular, this analysis demonstrates that the impact of the introduction of a larger range of analyzed variables serves to generally increase the sustainability score of the solvent. Reasons for this are unclear but may be due to the introduction of additional variables that tend to score highly for most solvents, such as reactivity/stability (GSK 2011: >75% of solvents scored ≥8/10 for this criterion), which may lead to a skewed average sustainability score.

Taking the information available in all of these published guides, a more holistic solvent selection guide is shown in **Table 2**, along with suggested alternatives to assist in supplanting a range of less desirable solvents (**Table 3**). A point to note is that some suggested alternatives

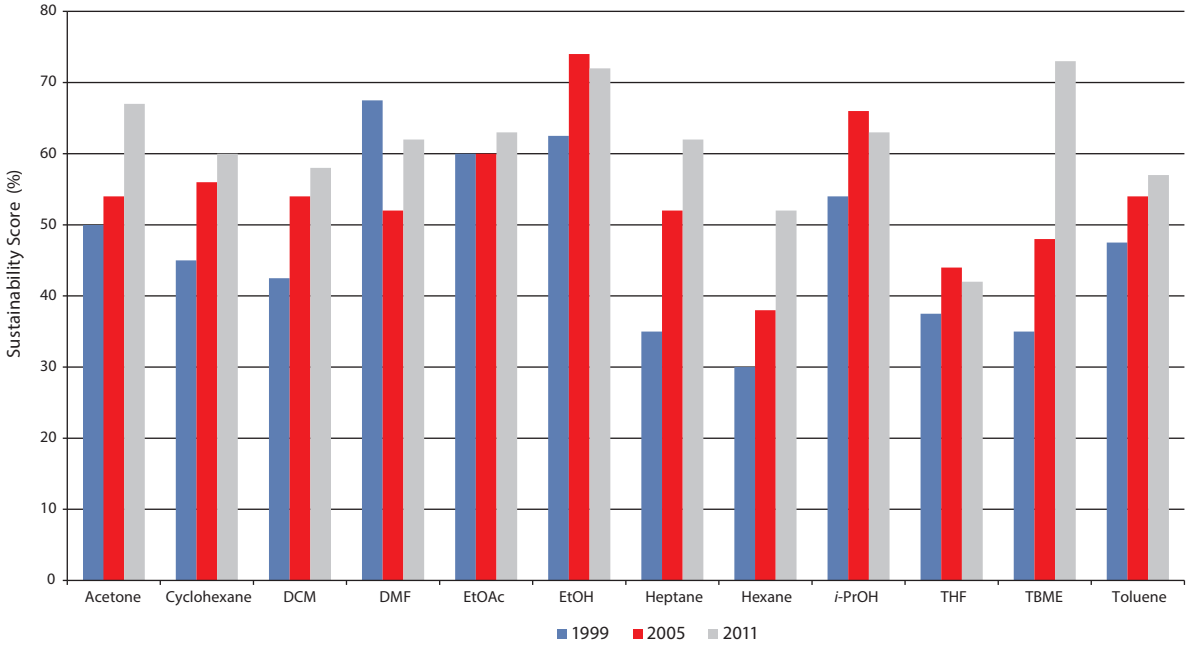
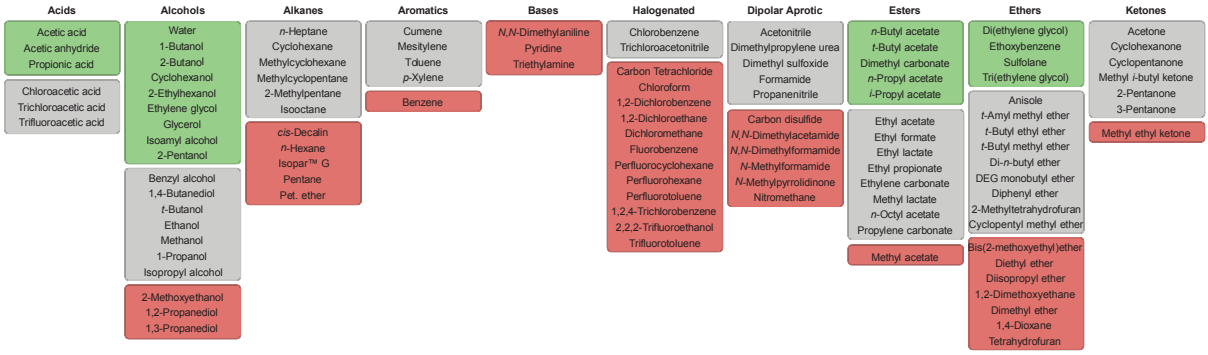


Figure 1. Evolution of GSK's Sustainability Score of 12 Selected Solvents from 1999 to 2011. *(Ref. 5)*

Table 2. A Summarized Solvent Selection Guide Based on the Analyses by GSK, Pfizer, and Sanofi. (Color key: red, solvents that should be avoided where possible; gray, solvents with some issues; green, solvents that are preferred.)



are not necessarily desirable themselves, but are preferred relative to the progenitor system for which a replacement is sought. For example, CH_2Cl_2 should be used as a replacement for $CHCl_3$, CCl_4, or DCE only where no other options are available.

2.2. Task-Specific Solvent Selection Guides

2.2.1. Chromatography

Chromatographic purification has been identified as the largest consumer of solvent within common synthetic processes.[3] Accordingly, adopting green chemistry principles within chromatography could have a significant impact on the overall sustainability of a chemical process without requiring substantial investment in terms of reaction development or optimization. In the 1960s, Neher published the first widely used equielutropic series that assisted in the identification of equipolar eluent systems for chromatographic purification.[15] Sustainability, however, was not necessarily a prevailing concern at the time, and this series was largely based upon solvents that are not in keeping with current green chemistry principles (for example, chlorinated solvents, hexane).

In the past few years, two studies—one from a group of industrial chemists at Amgen[10a] and the other from a collaboration between an academic group at the University of Strathclyde, GlaxoSmithKline (GSK), and Sigma-Aldrich (SA)[9]—sought to provide some guidance toward improving solvent selection in this area. These studies specifically targeted the replacement of CH_2Cl_2, which is commonly used in conjunction with MeOH as a modifier for the purification of relatively polar compounds.

The Amgen study focused on the use of alcohol- (MeOH, EtOH, *i*-PrOH) and additive-modified (AcOH, NH_4OH) mixtures of heptanes, EtOAc, and *tert*-butyl methyl ether (TBME) for the purification of a range of 26 drug-like molecules on silica, and helpfully presented a modern equielutropic series based on these mixtures in comparison to MeOH–CH_2Cl_2.

The Strathclyde/GSK/SA group adopted a slightly different approach and focused on establishing a direct replacement for CH_2Cl_2 while retaining MeOH as the modifier. Ultimately, cyclopentyl methyl ether (CPME) was identified as a potential greener surrogate for CH_2Cl_2, providing comparable and, in some cases improved, chromatographic results on normal silica gel. Similarly to the Amgen approach, this study also evaluated their suggested replacement solvent system on a 95-member library of drug-like and fragment compounds.

Both of these studies provided the first guidance for identifying eluents that can be used in a practical sense to replace CH_2Cl_2 in chromatography (i.e., utilizing a broad range of real examples). A summary of this guidance is provided in **Table 4**.[9]

Table 3. Suggested Alternatives to Undesirable Solvents

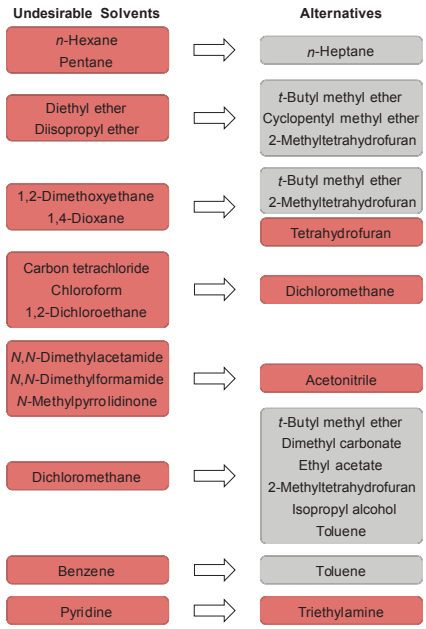
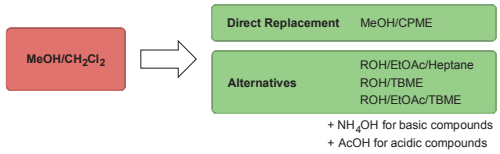


Table 4. Replacement of Dichloromethane in Chromatographic Purification *(Ref. 9)*

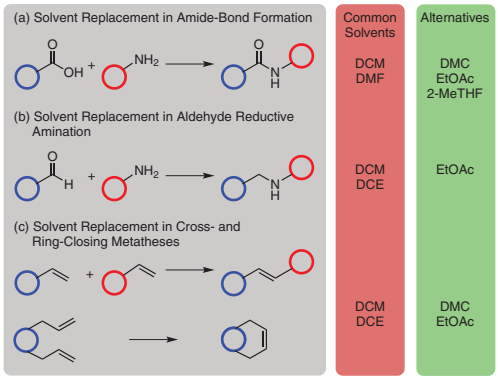


2.2.2. Reaction-Specific Solvent Selection Guides

Over the past few years, several studies have emerged that evaluate the performance of a range of established or emerging alternative solvents within widely used chemical transformations.[11–13] Many of the most common organic reactions employ solvents that have considerable issues from the sustainability perspective—DMF and chlorinated solvents in particular. As such, the primary aim of these reaction-specific investigations has been to establish the best alternative media without compromising the chemistry either from an efficiency perspective (i.e., yield) or from a practical viewpoint (i.e., setup, temperature, time, etc.).

Amide-bond formation is one of the most widely practiced organic reactions.[16,17] Indeed, a 2011 survey of the types of reaction used by industrial practitioners found that amidation accounted for approximately 16–17% of all transformations carried out in a medicinal chemistry environment.[16,17] In addition, DMF remains the solvent of choice for the majority of amide-bond-forming processes, and, for this reason, an effort was undertaken to provide a general alternative to DMF (as well as CH_2Cl_2) for amide-bond-forming reactions. The resulting comprehensive survey of eight alternative solvents within four benchmark reactions (aryl acid–aryl amine, aryl acid–alkyl amine, alkyl acid–aryl amine, and alkyl acid–alkyl amine) and using five common amidation reagents found that dimethyl carbonate (DMC), EtOAc, and 2-MeTHF are viable alternatives (**Scheme 1**, Part (a)).[11] This study also compared the reaction time in order to demonstrate the utility of the proposed replacements, alongside CH_2Cl_2 and DMF, in a representative application using amines and carboxylic acids that displayed the functionality common to Discovery Phase Medicinal Chemistry.

A similar analysis from the same research team was performed on another staple of industrial organic synthesis—reductive amination.[12] Similarly to amidation processes, reductive amination is broadly utilized[16,17] but has a heavy reliance on the use of chlorinated solvents, such as CH_2Cl_2 and DCE.[12] A thorough investigation of 12 benchmark reactions—employing representative examples of 12 amine classes in reductive amination with both alkyl and aryl aldehydes and using three different reductants and 10 solvents—found EtOAc to be a suitable replacement solvent in these reactions (Scheme 1, Part (b)).[12] Once more, the generality of these alternative conditions was exemplified through application to a set of 21 amine syntheses with an indication of reaction efficiency.



Scheme 1. Solvent Replacement in Common Organic Reactions. *(Ref. 11–13)*

The replacement of chlorinated solvents within key reactions continues to be a strong theme for research. Olefin metathesis is another key organic transformation that routinely employs chlorinated solvents. It was recently shown that CH_2Cl_2 could be replaced, once more, with EtOAc and DMC for cross-metathesis and ring-closing metathesis reactions (Scheme 1, Part (c)).[13]

3. Conclusions and Outlook

Over the past 15 years, a combination of industrial and academic research has provided a series of guides that have been designed to assist the practitioner with the selection of a more sustainable solvent for synthetic transformations. Of particular interest has been the replacement of solvents that are viewed as particularly problematic from a sustainability perspective—especially DMF and chlorinated solvents. As new guidance emerges and new alternative solvents researched and discovered, the identification of alternative solvents suitable for supplanting other problematic media will no doubt continue.

Indeed, beyond the guides described above, Grignard additions have recently been shown to be effective using deep eutectic solvents as a replacement for conventional ethereal solvents, as well as requiring a less stringent reaction setup: at room temperature and using air as the atmosphere.[18] Moreover, a series of specific guides and more general information on the selection of greener *reagents* for reactions are beginning to emerge, allowing facile selection not only of greener solvents for reactions but also of the reagents needed.[6,19]

4. Acknowledgments

We thank Dr. Helen F. Sneddon, GlaxoSmithKline, and Dr. Jane Murray, Sigma-Aldrich, for their support of our sustainable chemistry program.

5. References

(1) For selected books on the topic of Green Chemistry, see: (a) *Green Techniques for Organic Synthesis and Medicinal Chemistry*; Zhang, W., Cue, B. W., Jr., Eds.; Wiley: Chichester, U.K., 2012. (b) Jiménez-González, C.; Constable, D. J. C. *Green Chemistry and Engineering: A Practical Design Approach*; Wiley: Hoboken, NJ, 2011. (c) *Green Chemistry in the Pharmaceutical Industry*; Dunn, P. J., Wells, A. S., Williams, M. T., Eds.; Wiley-VCH: Weinheim, Germany, 2010. (d) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 2000.

(2) Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; Sneddon, H. F. *J. Med. Chem.* **2013**, *56*, 6007.

(3) Constable, D. J. C.; Jiménez-González, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, *11*, 133.

(4) For a survey of solvent selection guides, see Prat, D.; Hayler, J.; Wells, A. *Green Chem.* **2014**, *16*, 4546.

(5) (a) Curzons, A. D.; Constable, D. C.; Cunningham, V. L. *Clean Prod. Processes* **1999**, *1*, 82. (b) Jiménez-González, C.; Curzons, A. D.; Constable, D. J. C.; Cunningham, V. L. *Clean Technol. Environ. Policy* **2005**, *7*, 42. (c) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. *Green Chem.* **2011**, *13*, 854.

(6) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green. Chem.* **2008**, *10*, 31.

(7) Prat, D.; Pardigon, O.; Flemming, H.-W.; Letestu, S.; Ducandas, V.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S.; Cruciani, P.; Hosek, P. *Org. Process Res. Dev.* **2013**, *17*, 1517.

(8) For AstraZeneca's guide, see Hargreaves, C. R.; Manley, J. B. ACS

GCI Pharmaceutical Roundtable: Collaboration to Deliver a Solvent Selection Guide for the Pharmaceutical Industry, 2008. ACS Green Chemistry Institute® Web site. http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/solvent-selection-guide.pdf (accessed April 13, 2015).

(9) MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. *Green Chem.* **2012**, *14*, 3016.

(10) (a) Taygerly, J. P.; Miller, L. M.; Yee, A.; Peterson, E. A. *Green Chem.* **2012**, *14*, 3020. (b) Peterson, E. A.; Dillon, B.; Raheem, I.; Richardson, P.; Richter, D.; Schmidt, R.; Sneddon, H. F. *Green Chem.* **2014**, *16*, 4060.

(11) MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. *Green Chem.* **2013**, *15*, 596.

(12) McGonagle, F. I.; MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. *Green Chem.* **2013**, *15*, 1159.

(13) Skowerski, K.; Białecki, J.; Tracz, A.; Olszewski, T. K. *Green Chem.* **2014**, *16*, 1125.

(14) For a recent review of LCA, see Jiménez-González, C.; Overcash, M. R. *Green Chem.* **2014**, *16*, 3392.

(15) Neher, R. In *Thin Layer Chromatography*; Marini-Bettolo, G. B., Ed.; Elsevier: Amsterdam, The Netherlands, 1964; pp 75–86.

(16) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.

(17) Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 8082.

(18) Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A. R.; Hevia, E. *Angew. Chem., Int. Ed.* **2014**, *53*, 5969.

(19) (a) Adams, J. P.; Alder, C. M.; Andrews, I.; Bullion, A. M.; Campbell-Crawford, M.; Darcy, M. G.; Hayler, J. D.; Henderson, R. K.; Oare, C. A.; Pendrak, I.; Redman, A. M.; Shuster, L. E.; Sneddon, H. F.; Walker, M. D. *Green Chem.* **2013**, *15*, 1542. (b) Henderson, R. K.; Hill, A. P.; Redman, A. M.; Sneddon, H. F. *Green Chem.* **2015**, *17*, 945.

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Harry Eastman was born in 1992 in Portsmouth, England, U.K. He studied chemistry at the University of Surrey, working for a year with Professor A. M. P. Koskinen at Aalto University, and completed an M.Sci. degree in Chemistry program in 2014. He began his Ph.D. studies with Dr. Allan Watson in 2014, and is currently focused on the development of new methods for organic synthesis.

Craig Jamieson earned his B.Sc. (Hons) in Chemistry degree at the University of Glasgow in 1996. His Ph.D. studies were carried out under the direction of Professor R. Ramage at the University of Edinburgh (1999). Following postdoctoral research under the supervision of Professor S. V. Ley at the University of Cambridge, he was appointed in 2001 as Principal Scientist in GlaxoSmithKline's Discovery Medicinal Chemistry group, where he worked on a range of exploratory medicinal chemistry programs. In 2004, Craig joined Organon Laboratories (later Merck Research Labs) as a Group Leader in the Medicinal Chemistry Department, with responsibility for hit-to-clinical candidate optimization. In August 2010, he accepted an appointment as John Anderson Research Lecturer in Chemical Biology in the Department of Pure and Applied Chemistry at the University of Strathclyde.

Allan J. B. Watson obtained his M.Sci. degree in 2004 from the University of Strathclyde and his Ph.D. degree (with Professor W. J. Kerr) in 2008. This was followed by postdoctoral work with Professor D. W. C. MacMillan at Princeton University, and an industrial postdoctoral research position at GlaxoSmithKline. He returned to a lecturer position at the University of Strathclyde in 2011. His research interests are synthetic methodology, boron chemistry, medicinal chemistry, and sustainable synthesis.

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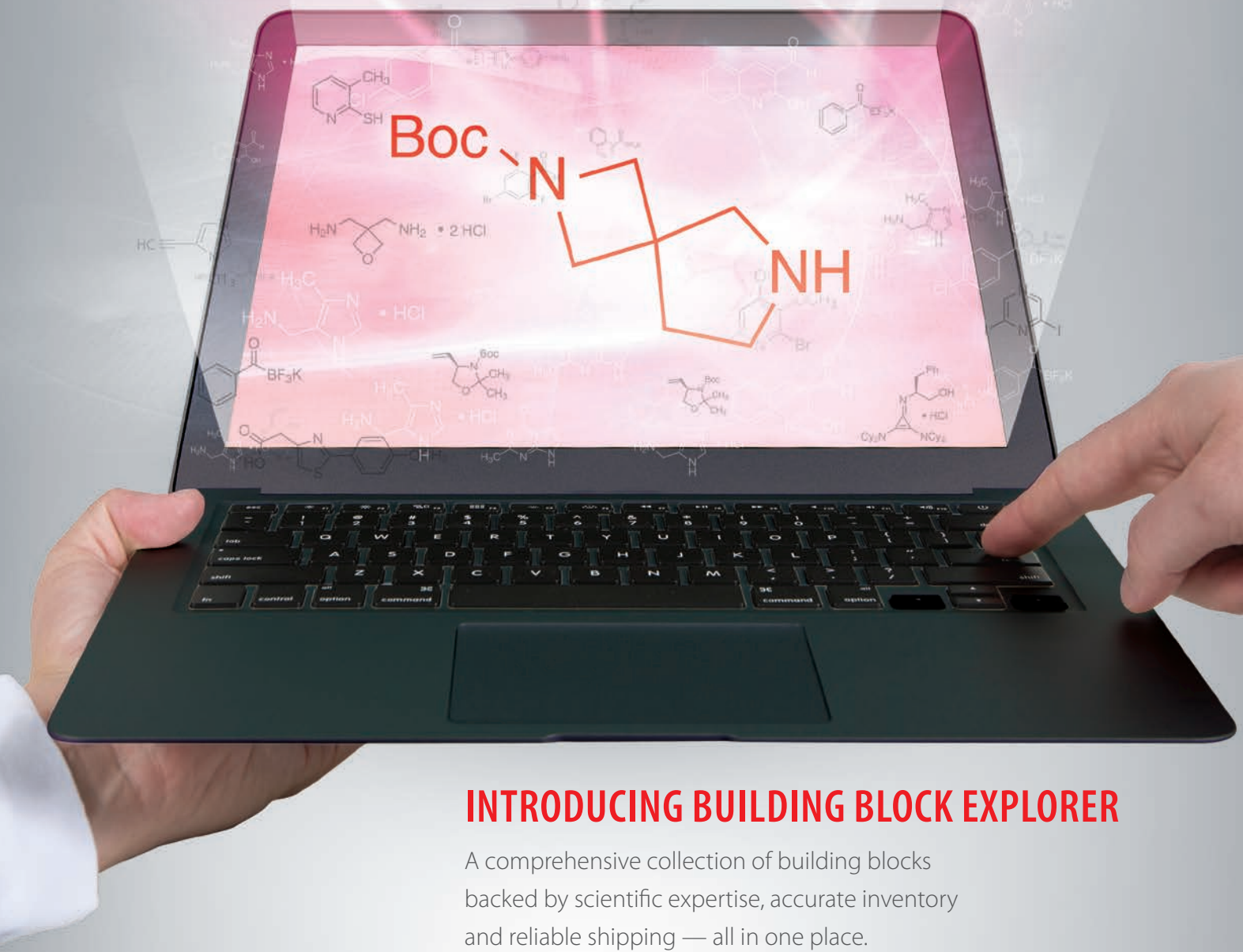

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