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Organic Synthesis

Octahedral Chiral-at-Metal Iridium Catalysts: Versatile Chiral Lewis Acids for Asymmetric Conjugate Additions

Xiaodong Shen,[a] Haohua Huo,[a] Chuanyong Wang,[a] Bo Zhang,[a] Klaus Harms,[a] and Eric Meggers*[a, b]

Abstract: Octahedral iridium(III) complexes containing two bidentate cyclometalating 5-*tert*-butyl-2-phenylbenzoxazole (**IrO**) or 5-*tert*-butyl-2-phenylbenzothiazole (**IrS**) ligands in addition to two labile acetonitrile ligands are demonstrated to constitute a highly versatile class of asymmetric Lewis acid catalysts. These complexes feature the metal center as the exclusive source of chirality and serve as effective asymmetric catalysts (0.5–5.0 mol% catalyst loading) for a variety of reactions with α,β-unsaturated carbonyl compounds, namely Friedel–Crafts alkylations (94–99% *ee*), Michael additions with CH-acidic compounds (81–97% *ee*), and a variety of cycloadditions (92–99% *ee* with high d.r.). Mechanistic investigations and crystal structures of an iridium-coordinated substrates and iridium-coordinated products are consistent with a mechanistic picture in which the α,β-unsaturated carbonyl compounds are activated by two-point binding (bidentate coordination) to the chiral Lewis acid.

Introduction

Metal-based asymmetric catalysts are typically constructed from a central metal ion in combination with one or multiple chiral ligands so that the catalysts chirality originates from one or more carbon, sulfur and/or phosphorus stereogenic centers in the ligand sphere.[1] In contrast, asymmetric catalysts that draw their chirality exclusively from a chiral metal center[2] are much less investigated although such catalysts might display some attractive features, such as structural simplicity (only achiral ligands required) and an effective chirality transfer in the course of the reaction due to the direct proximity of the metal-based stereocenter to the metal-coordinating substrate.[3] Synthetic challenges have hampered the development of such chiral-at-metal catalysts in the past but were overcome by our previously introduced methodology of employing coordinating chiral auxiliaries[4] for a convenient synthesis of enantiopure octahedral chiral-at-metal ruthenium(II),[5] rhodium(III),[6] and iridium(III)[7] complexes, and opened up new avenues for the straightforward design of highly powerful chiral-only-at-metal asymmetric catalysts.[8]

Many functional groups in organic chemistry are amenable to Lewis acid activation in a straightforward and predictable fashion and chiral Lewis acids are, therefore, attractive tools for effective asymmetric catalysis.[9] One highly appealing goal in this area of research is the development of chiral Lewis acid catalysts that exhibit a broad generality with respect to reaction types and substrates. Recently, we introduced octahedral iridium(III) and rhodium(III) complexes as a novel class of chiral Lewis acid catalysts.[6,10,11] In these complexes, the octahedral metal center is coordinated irreversibly by two cyclometalating bidentate ligands in a propeller-type fashion. Two additional exchange-labile coordinated acetonitriles allow substrates to become activated by two-point binding. These complexes are structurally quite simple and only contain achiral ligands, with metal-centered chirality (metal centrochirality) being the exclusive source of chirality.[2] Importantly, despite the two labile acetonitrile ligands, the catalysts are configurationally inert and retain their relative and absolute configurations throughout the catalysis. In this work, we demonstrate the high versatility of the iridium(III) complexes Λ-**IrO**[10] and Λ-**IrS**[11] (Figure 1) as chiral Lewis acid catalysts for a variety of asymmetric reactions with acceptor-substituted alkenes, including

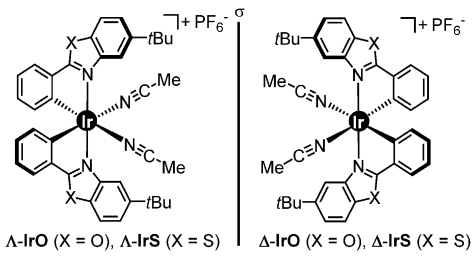

Figure 1. Chiral-at-metal Lewis acid catalysts used in this study. Note that the metal center constitutes the exclusive source of chirality in these catalysts.

[a] X. Shen, H. Huo, C. Wang, B. Zhang, Dr. K. Harms, Prof. Dr. E. Meggers
Fachbereich Chemie, Philipps-Universität Marburg
Hans-Meerwein-Straße, 35043 Marburg (Germany)
E-mail: meggers@chemie.uni-marburg.de

[b] Prof. Dr. E. Meggers
College of Chemistry and Chemical Engineering
Xiamen University, Xiamen 361005, (P. R. China)

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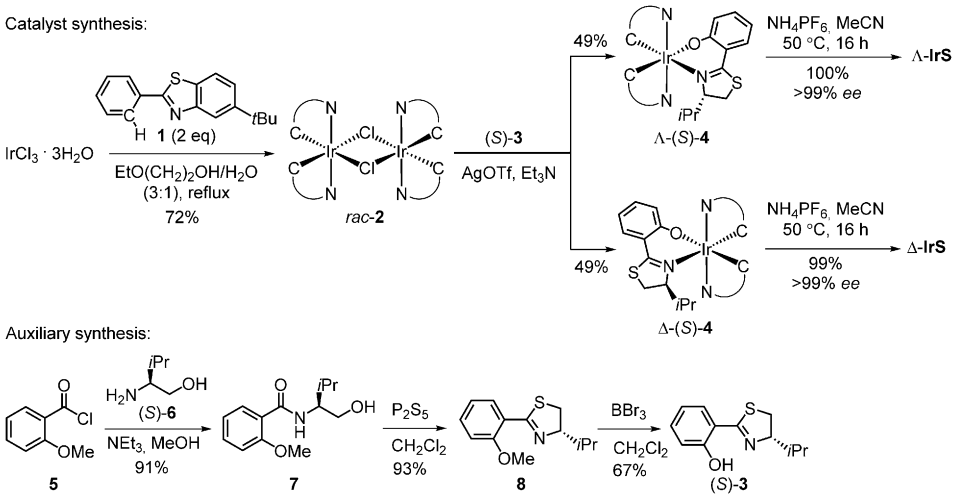
Friedel–Crafts alkylations, Michael additions with CH-acidic compounds, and cycloadditions.

Results and Discussion

Catalyst synthesis

The chiral-at-metal catalysts can be synthesized with high enantiomeric purity through a convenient auxiliary-mediated strategy developed in our laboratory,[7] as shown for the synthesis of Λ-**IrS** and Δ-**IrS** in Scheme 1. Accordingly, $IrCl_3$ hydrate is reacted with 5-*tert*-butyl-2-phenylbenzothiazole (**1**), synthesized itself in two steps from 1-bromo-4-*tert*-butylbenzene,[12] in 2-ethoxyethanol/water 3:1 under reflux to provide the iridium dimer complex *rac*-**2** in a diastereoselective fashion.[13] The subsequent reaction with the chiral auxiliary ligand (*S*)-4-isopropyl-2-(2′-hydroxyphenyl)-2-thiazoline ((*S*)-**3**) affords the iridium(III) complexes Λ-(*S*)-**4** and Δ-(*S*)-**4** as a mixture of diastereomers, which can be resolved easily by standard silica gel chromatography on a gram scale.[11] Upon reaction in acetonitrile in the presence of the weak acid NH_4PF_6 and at slightly elevated temperature (50 °C), these complexes are converted to virtually enantiopure complexes Λ-**IrS** and Δ-**IrS** (each >99% *ee*) by a stereospecific substitution of the (protonated) chiral auxiliary with two acetonitrile ligands under retention of configuration. It is noteworthy that the chiral auxiliary can be recovered after this reaction in high yield (96%) and without any loss of enantiomeric purity (≥99.9% *ee*). The enantiomeric purity of Λ-**IrS** and Δ-**IrS** was verified by HPLC on a chiral stationary phase. No noticeable loss in catalytic performance can be observed upon storage under argon in a refrigerator (5 °C) for several months. The chiral auxiliary (*S*)-**3** can be synthesized in three steps starting from acid chloride **5** in an overall yield of 57%: Reaction with the chiral amino alcohol (*S*)-**6** affords amide **7** (91%), which is cyclized to the thiazoline **8** with P_2S_5 (93%), followed by ether cleavage with BBr_3 (67%).



Scheme 1. Auxiliary-mediated synthesis of the enantiomerically pure chiral-at-metal iridium(III) complexes Λ-**IrS** and Δ-**IrS**.

Asymmetric Friedel–Crafts alkylations

We recently reported that Λ- and Δ-**IrO** can efficiently catalyze the enantioselective Friedel–Crafts addition of indoles to α,β-unsaturated 2-acyl imidazoles.[10] We were speculating that the derivative Λ- and Δ-**IrS**,[11] in which the cyclometalated 2-phenylbenzoxazole is replaced by a 2-phenylbenzothiazole, would be able to provide a higher asymmetric induction due to the long C–S bonds that position the two *tert*-butyl groups closer to the two vacant coordination sites. And indeed, when we evaluated Λ-**IrS** (1.0 mol%) for the Friedel–Crafts alkylation of indole with 2-acyl imidazole **9a**, the expected alkylation product (*S*)-**10** was obtained with 99% *ee* at room temperature compared to 96% *ee* for Λ-**IrO** (as shown in Figure 2).[14,15] This trend holds for the Friedel–Crafts reaction with 3-dimethylaminoanisole, for which Λ-**IrS** (2.0 mol%) affords (*S*)-**11a** in 97% yield and with excellent 99% *ee*, compared to 94% *ee* when using Λ-**IrO** (2 mol%) instead. In contrast, for 2-methoxyfurane[15a,b] and pyrrole[15a,b,16] the respective Friedel–Crafts products (*S*)-**12** and (*S*)-**13** were obtained with almost equal enantioselectivities (as shown in Figure 2). Overall, compared to Λ-**IrO**, Λ-**IrS** generally requires somewhat elongated reaction times that can be attributed to the larger steric hindrance around the coordination sites.[17] However, the reactions can be accelerated by raising the temperature without affecting much the enantioselectivity. For example, increasing the temperature for the reaction **9a**→(*S*)-

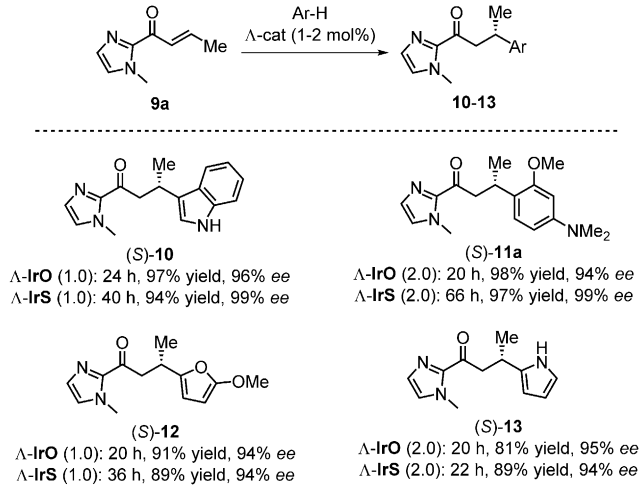


Figure 2. Chiral octahedral iridium(III) Lewis acid catalysis applied to Friedel–Crafts alkylations with α,β-unsaturated 2-acyl imidazole **9a**.

Table 1. Friedel–Crafts alkylation with α,β-unsaturated 2-acyl imidazoles: Effects of substituents, catalyst loading, and temperature.[a]

Substrate	Product	Cat. loading [mol%]	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
R = Me (**9a**)	(*S*)-**11a**	2.0	RT	66	97	99
			30	48	94	99
			40	25	95 (83)[d]	99 (99)[d]
			50	< 20	99	98
			60	5	96	98
		0.5	40	32	96	98
R = Ph (**9b**)	(*R*)-**11b**	2.0	40	18	99	99
R = CO_2Et (**9c**)	(*S*)-**11c**	2.0	40	24	95	99
R = *n*Bu (**9d**)	(*S*)-**11d**	2.0	40	48	81	96

[a] Reaction conditions: 2-acyl imidazoles **9a–d** (0.20 mmol), 3-dimethylaminoanisole (0.60 mol), THF (0.1 mL). [b] Isolated yields. [c] Enantiomeric excess determined by HPLC analysis on chiral stationary phase. [d] Yield and enantioselectivity for the analogous reaction performed under air shown in brackets.

11a from room temperature to 60 °C leads to full conversion in just 5 h with only a slightly diminished enantioselectivity of 98% *ee* (Table 1). Interestingly, the reaction is insensitive to air (Table 1). It is also noteworthy that the catalyst loading can be decreased for this reaction to 0.5 mol% and that the acyl imidazole substrates **9b–d** also provide the respective Friedel–Crafts alkylation products (*R*)-**11b**, (*S*)-**11c**, and (*S*)-**11d** with high enantioselectivities (Table 1).

Asymmetric Michael additions

Next, we investigated the addition of CH-acidic malonodinitrile and 1,3-dicarbonyl compounds to the Michael acceptor **9a** as shown in Figure 3. By using Λ-**IrS** at a loading of 1.0 or 2.0 mol%, the malonodinitrile[18] addition product (*S*)-**14** was formed in a yield of 95% with 90% *ee* and the Meldrum's acid addition product (*S*)-**15** in a yield of 94% with 91% *ee*. Λ-**IrS** is also suitable to catalyze the formation of an all-carbon quaternary stereocenter[19] as the reaction of *tert*-butyl 2-oxocyclopentane-1-carboxylate with 2-acyl imidazole **9a** afforded (*S*,*S*)-**16** in 85% yield, with 96% *ee*, and 1.5:1 d.r.. The related Michael addition of 2,3-dihydro-1-oxo-1*H*-indene-2-carboxylic acid *tert*-butyl ester to 2-acyl imidazole **9a** provided (*S*,*S*)-**17** in 93% yield with 97% *ee* and 22:1 d.r.. As found for the Friedel–Crafts reactions, the stereoselectivity of the related catalyst Λ-**IrO** was generally slightly lower.

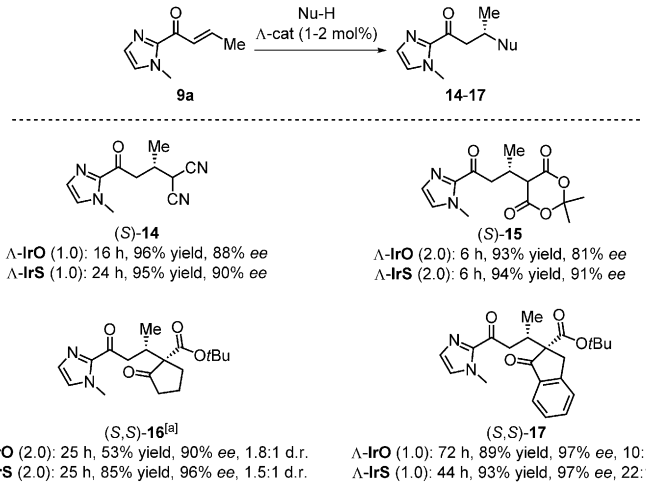


Figure 3. Chiral octahedral iridium(III) Lewis acid catalysis applied to Michael additions with α,β-unsaturated 2-acyl imidazole **9a**. [a] Reaction performed at 40 °C instead of room temperature.

Asymmetric cycloadditions

We next investigated cycloadditions with α,β-unsaturated 2-acyl imidazoles (Figure 4). Accordingly, the reaction of **9a** with the nitrone **18** catalyzed by 2.0 mol% of Λ-**IrS** provided the 1,3-dipolar cycloaddition product **19** in a yield of 86% and with excellent 98% *ee*, while virtually forming just one diastereomer (*endo*/*exo* > 100:1).[20,21] The enantioselectivity was significantly lower using Λ-**IrO** (92% *ee*). In contrast, for the hetero-Diels–Alder reaction between **9a** or **9e** with 2,3-dihydrofurane under formation of the dihydropyrans **20** and **21**, respectively, Λ-**IrO** (2 mol%) turned out to be the catalyst of choice, providing high diastereo- and enantioselectivities.[22,23] At last, the Diels-Alder reaction of **9a** with isoprene provided the desired product **22** with high enantio- and diastereoselectivity.[24]

Scope of acceptor-substituted alkenes

After we revealed that **IrO** and **IrS** catalyze the asymmetric conjugate addition of a wide variety of nucleophiles to α,β-unsaturated 2-acyl imidazoles, we next investigated the scope with respect to acceptor substituted alkenes and used the enantioselective Friedel–Crafts alkylation with 3-dimethylaminoanisole as our model reaction (Figure 5). We were pleased to find that a significant number of the tested acceptor-substituted alkenes **9f–p**[15a,b,25–33] proved to be suitable substrates, providing the expected products in high yields and high enantioselectivities, such as the benzimidazole **9f** (86% yield, 96% *ee*),[25] 2-thiazole **9g** (99% yield, 98% *ee*),[26] pyridine **9h** (87% yield, 97% *ee*),[27] pyrazoles **9k** (86% yield, 98% *ee*), and **9l** (99% yield, 95% *ee*),[30] and α-ketoester **9n** (99% yield, 95% *ee*).[32] Apparently, only substrates that can efficiently coordinate to the iridium catalyst in a bidentate fashion give satisfactory results, whereas the simple α,β-unsaturated carboxylic ester **9p** does not afford any product even at higher catalyst loadings of 5 mol% and an elevated temperature of 60 °C. On the other hand, we do not have an explanation for

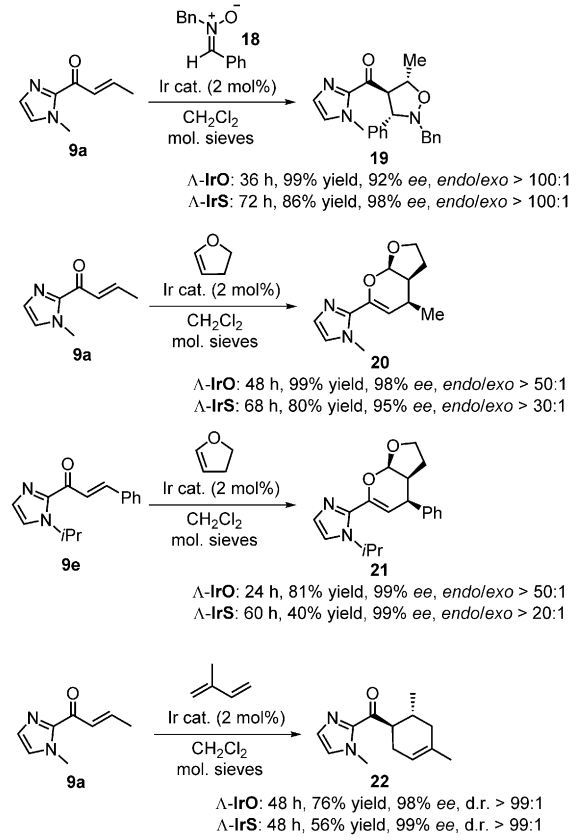


Figure 4. Chiral octahedral iridium(III) Lewis acid catalysis applied to cycloadditions with α,β-unsaturated 2-acyl imidazoles.

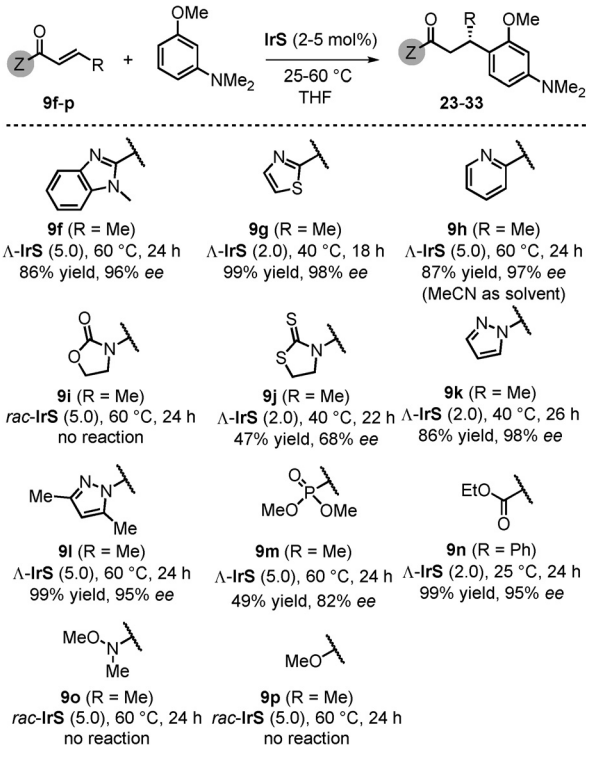


Figure 5. Substrate scope with respect to electron acceptor substituted alkenes.

the failing or sluggish conversion of some of the other substrates such as the 2-oxazolidinone **9i**,[28] 2-thiazolidinethione **9j**,[29] phosphonate **9m**,[31] and Weinreb amide **9o**.[33] However, we believe that the addition to α,β-unsaturated ketoesters,[32] α,β-unsaturated *N*-acyl pyrazoles,[30] α,β-unsaturated 2-acyl thiazoles[26,8c] and α,β-unsaturated 2-acyl imidazoles[34] are particularly useful substrates since they are easily converted to a variety of different carbonyl compounds.

Mechanistic considerations

It is plausible that the catalytic cycle starts with the bidentate coordination of the α,β-unsaturated carbonyl compound to the catalyst through the carbonyl and one additional moiety (e.g. imidazole, benzimidazole, pyrazole, pyridine, or carboxylic ester) under release of the two labile acetonitrile ligands, thereby leading to the intermediate **A** (Figure 6). This two-

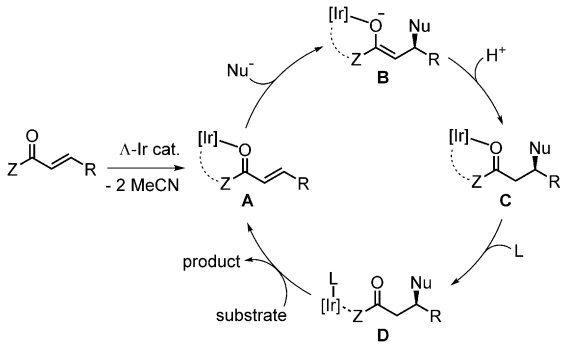


Figure 6. Plausible mechanistic cycle for the reported asymmetric Lewis acid catalysis.

point binding of the substrate increases the electrophilicity of the double bond and promotes a nucleophilic addition to the β-position of the alkene. Figure 7a displays a crystal structure of such an intermediate **A**, namely the substrate **9e** coordinated to Λ-**IrO**. The space filling model of this structure also convincingly illustrates that the prochiral *Si*-face is shielded by one *tert*-butyl group and therefore guides the nucleophilic addition to the *Re*-face. This is consistent with the obtained absolute configuration of the addition products and leads to the intermediate enolate complex **B**, which after protonation, provides the bidentate coordinated substrate (intermediate **C**). The replacement of the coordinated product by a new substrate, followed by a new catalytic cycle, presumably occurs through an intermediate in which the product is monocoordinated (intermediate **D**) and the sixth coordinate site either filled by acetonitrile or the new substrate. We were able to trap such formed iridium coordinated product for the conversion **9e**→**21**. Figure 7b shows that the cycloaddition product **21** is coordinated to the catalyst through the imidazole moiety and an acetonitrile ligand is filling the remaining coordination sphere.

Finally, kinetic experiments (Figure 8) performed with the reaction **9a**→**11a** revealed that the rate of the overall catalysis does not depend on the concentration of the nucleophile 3-dimethylaminoanisole but is directly proportional to the concen-

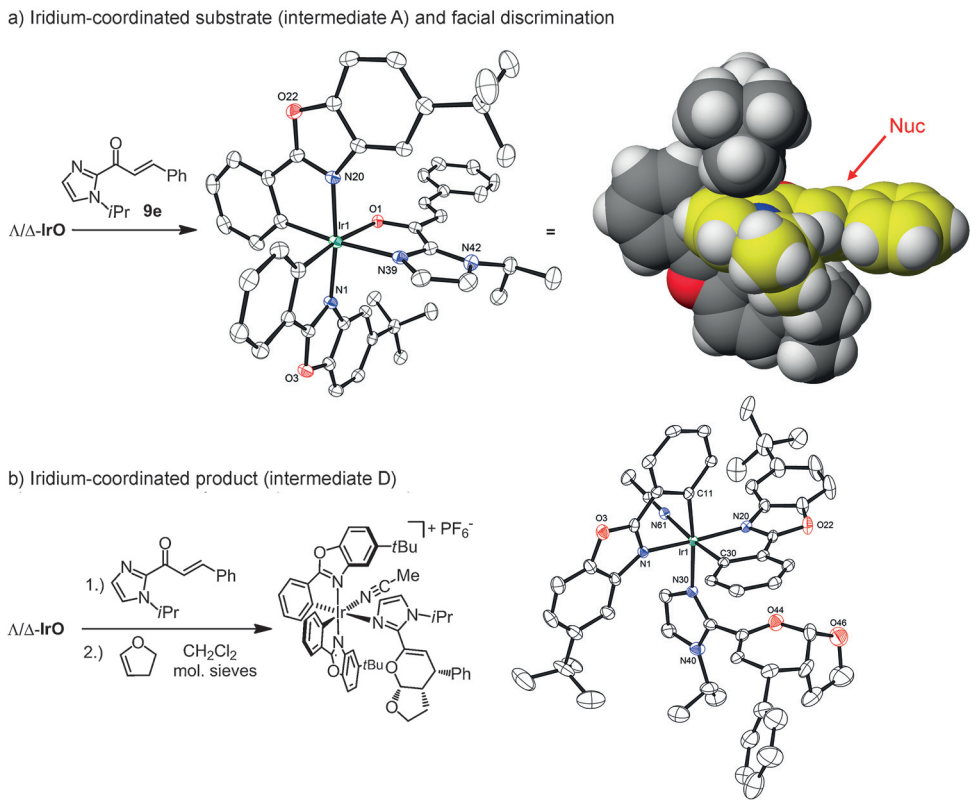


Figure 7. a) Crystal structure obtained upon reaction of Λ/Δ-**IrO** with the substrate **9e**. See the Supporting Information for more details. Only the Λ-enantiomer is shown and the hexafluorophosphate counteranion is omitted for clarity. ORTEP drawing with 50% probability thermal ellipsoids and space filling representation with an adjusted orientation. b) Crystal structure obtained upon the reaction of racemic Λ/Δ-**IrO** with substrate **9e** overnight, followed by the addition of 2,3-dihydrofurane. See the Supporting Information for more details. Only the Δ-enantiomer is shown and the hexafluorophosphate counteranion is omitted for clarity. ORTEP drawing with 50% probability thermal ellipsoids.

tration of the α,β-unsaturated 2-acyl imidazole **9a**, thus demonstrating that the rate-determining step cannot be the nucleophilic addition to the iridium-coordinated substrate (conversion **A**→**B** in Figure 6) but instead must be the replacement of iridium-coordinated product with a new substrate molecule (conversion **D**→**A** in Figure 6). This is not unexpected because of the well-known kinetic stability of coordinative bonds to iridium(III) in octahedral complexes.

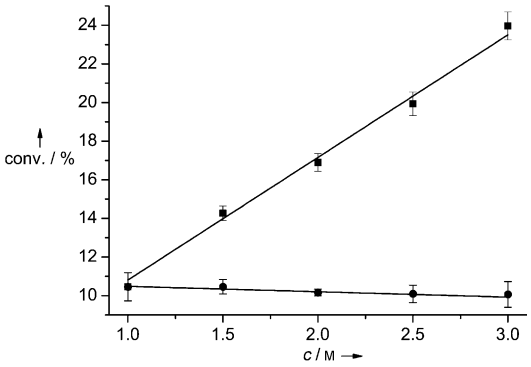


Figure 8. Kinetic experiments to get insight into the rate-determining step. Dependence of the conversion **9a**→**11a** as a function of changing the concentration of one substrate while keeping the other substrate constant using *rac*-**IrS** (2 mol%) in anhydrous THF at room temperature for 2 h. ■: acyl imidazole **9a**, ●: 3-dimethylaminoanisole.

Conclusion

In summary, the reactions discussed here reveal the versatility of the chiral-at-metal iridium(III) catalysts. It is quite remarkable that a single class of chiral Lewis acid catalysts is capable of effectively catalyzing different reaction types, as demonstrated for Friedel–Crafts reactions, Michael additions of CH-acidic compounds, and a variety of cycloadditions. A significant variability also exists with respect to the α,β-unsaturated carbonyl substrates as long as they allow a two-point binding to the iridium catalyst. We are convinced that this novel class of chiral-only-at-metal catalysts are of significant practical value as they are accessible in a straightforward fashion, are unproblematic for long-term storage, provide excellent yields and asymmetric inductions at low catalyst loadings, can be used at room temperature or slightly elevated temperatures, and do not require a stringent exclusion of air and moisture. It has to be noted that in a previous study we established that the rhodium congener of Λ- and Δ-**IrO** is a somewhat superior catalyst for Michael additions with CH-acidic compounds.[6] However, the cost for rhodium is currently significantly higher compared to iridium which most likely renders the iridium complexes the catalysts of choice for the here presented reactions.

Keywords: asymmetric catalysis · chiral-at-metal · conjugate addition · iridium · Lewis acid

[1] P. J. Walsh, M. C. Kozlowski, *Fundamentals of Asymmetric Catalysis*; University Science Books, Sausalito, California, **2009**.

[2] For reviews on different aspects of metal-centered chirality, see: a) J.-L. Pierre, *Coord. Chem. Rev.* **1998**, *178–180*, 1183–1192; b) U. Knof, A. von Zelewsky, *Angew. Chem. Int. Ed.* **1999**, *38*, 302–322; *Angew. Chem.* **1999**, *111*, 312–333; c) P. D. Knight, P. Scott, *Coord. Chem. Rev.* **2003**, *242*, 125–143; d) H. Amouri, M. Gruselle, *Chirality in Transition Metal Chemistry*, Wiley, Chichester, UK, **2008**; e) E. Meggers, *Eur. J. Inorg. Chem.* **2011**, 2911–2926; f) J. Crassous, *Chem. Commun.* **2012**, *48*, 9684–9692; g) E. C. Constable, *Chem. Soc. Rev.* **2013**, *42*, 1637–1651.

[3] For reviews covering chiral-at-metal complexes and their catalytic applications, see: a) H. Brunner, *Angew. Chem. Int. Ed.* **1999**, *38*, 1194–1208; *Angew. Chem.* **1999**, *111*, 1248–1263; b) C. Ganter, *Chem. Soc. Rev.* **2003**, *32*, 130–138; c) M. Fontecave, O. Hamelin, S. Ménage, *Top. Organomet.*

Chem. **2005**, *15*, 271 – 288; d) E. B. Bauer, *Chem. Soc. Rev.* **2012**, *41*, 3153 – 3167; e) L. Gong, L.-A. Chen, E. Meggers, *Angew. Chem. Int. Ed.* **2014**, *53*, 10868 – 10874; *Angew. Chem.* **2014**, *126*, 11046 – 11053.

[4] E. Meggers, *Chem. Eur. J.* **2010**, *16*, 752 – 758.

[5] First report: L. Gong, S. P. Mulcahy, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2009**, *131*, 9602 – 9603. For a recent account, see: L. Gong, M. Wenzel, E. Meggers, *Acc. Chem. Res.* **2013**, *46*, 2635 – 2644.

[6] C. Wang, L.-A. Chen, H. Huo, X. Shen, K. Harms, L. Gong, E. Meggers, *Chem. Sci.* **2015**, *6*, 1094 – 1100.

[7] M. Helms, Z. Lin, L. Gong, K. Harms, E. Meggers, *Eur. J. Inorg. Chem.* **2013**, 4164 – 4172.

[8] a) L.-A. Chen, W. Xu, B. Huang, J. Ma, L. Wang, J. Xi, K. Harms, L. Gong, E. Meggers, *J. Am. Chem. Soc.* **2013**, *135*, 10598 – 10601; b) L.-A. Chen, X. Tang, J. Xi, W. Xu, L. Gong, E. Meggers, *Angew. Chem. Int. Ed.* **2013**, *52*, 14021 – 14025; *Angew. Chem.* **2013**, *125*, 14271 – 14275; c) J. Ma, X. Ding, Y. Hu, Y. Huang, L. Gong, E. Meggers, *Nat. Commun.* **2014**, *5*, 4531; d) H. Huo, C. Fu, C. Wang, K. Harms, E. Meggers, *Chem. Commun.* **2014**, *50*, 10409 – 10411.

[9] For reviews and accounts covering different aspects of chiral Lewis acid catalysis, see: a) K. Narasaka, *Synthesis* **1991**, 1 – 11; b) S. Saito, H. Yamamoto, *Chem. Commun.* **1997**, 1585 – 1592; c) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thorhauge, *Acc. Chem. Res.* **1999**, *32*, 605 – 613; d) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325 – 335; e) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561 – 3651; f) S. Kobayashi, C. Ogawa, *Chem. Eur. J.* **2006**, *12*, 5954 – 5960; g) S. Kanemasa, M. Hasegawa, F. Ono, *Chem. Rec.* **2007**, *7*, 137 – 149; h) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279 – 1300; i) M. North, D. L. Usanov, C. Young, *Chem. Rev.* **2008**, *108*, 5146 – 5226; j) P. Li, H. Yamamoto, *Top. Organomet. Chem.* **2011**, *37*, 161 – 183; k) J. Zhou, Y. Tang, *Top. Organomet. Chem.* **2011**, *36*, 287 – 312; l) L. C. Dias, E. C. de Lucca Jr., M. A. B. Ferreira, E. C. Polo, *J. Braz. Chem. Soc.* **2012**, *23*, 2137 – 2158; m) H. Yamamoto, *Top. Organomet. Chem.* **2013**, *44*, 315 – 334.

[10] H. Huo, C. Fu, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2014**, *136*, 2990 – 2993.

[11] H. Huo, X. Shen, C. Wang, L. Zhang, P. Röse, L.-A. Chen, K. Harms, M. Marsch, G. Hilt, E. Meggers, *Nature* **2014**, *515*, 100 – 103.

[12] A new redox condensation was used for the synthesis of benzothiazoles, see: T. B. Nguyen, L. Ermolenko, P. Retailleau, A. Al-Mourabit, *Angew. Chem. Int. Ed.* **2014**, *53*, 13808 – 13812; *Angew. Chem.* **2014**, *126*, 14028 – 14032.

[13] For related cyclometalation reactions with 2-phenylbenzothiazoles, see: S. Lamansky, P. Djurovich, D. Murphy, F. Abdel-Razzaq, R. Kwong, I. Tsyba, M. Bortz, B. Mui, R. Bau, M. E. Thompson, *Inorg. Chem.* **2001**, *40*, 1704 – 1711.

[14] For chiral octahedral iridium(III) complexes in asymmetric catalysis, see: a) P. Paredes, J. Díez, M. P. Gamasa, *Organometallics* **2008**, *27*, 2597 – 2607; b) C. P. Owens, A. Varela-Álvarez, V. Boyarskikh, D. G. Musaev, H. M. L. Davies, S. B. Blakey, *Chem. Sci.* **2013**, *4*, 2590 – 2596; c) D. Carmona, J. Ferrer, N. García, P. Ramírez, F. J. Lahoz, P. García-Orduña, L. A. Oro, *Organometallics* **2013**, *32*, 1609 – 1619; d) Y. Kita, K. Yamaji, K. Higashida, K. Sataiah, A. Iimuro, K. Mashima, *Chem. Eur. J.* **2015**, *21*, 1915 – 1927.

[15] For catalytic asymmetric Friedel–Crafts alkylations with α,β-unsaturated 2-acyl imidazoles, see: a) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942 – 8943; b) D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029 – 10041; c) A. J. Boersma, B. L. Feringa, G. Roelfes, *Angew. Chem. Int. Ed.* **2009**, *48*, 3346 – 3348; *Angew. Chem.* **2009**, *121*, 3396 – 3398; d) C. Wang, Y. Li, G. Jia, Y. Liu, S. Lu, C. Li, *Chem. Commun.* **2012**, *48*, 6232 – 6234; e) J. Wang, E. Benedetti, L. Bethge, S. Vonhoff, S. Klussmann, J.-J. Vasseur, J. Cossy, M. Smietana, S. Arseniyadis, *Angew. Chem. Int. Ed.* **2013**, *52*, 11546 – 11549; *Angew. Chem.* **2013**, *125*, 11760 – 11763.

[16] D. A. Evans, K. R. Fandrick, *Org. Lett.* **2006**, *8*, 2249 – 2252.

[17] Comparison with a bis(oxazolinyl)pyridine–scandium(III) triflate catalyst. Reaction with indole: 80% yield and 65% *ee* with 2.5 mol% catalyst at 0 °C (ref. [15a] and [15b]). Reaction with 3-dimethylaminoanisole: $<$20% yield and 22% *ee* (ref. [15b]). Reaction with 2-methoxyfurane: 65% yield and 98% *ee* with 2.0 mol% catalyst at -40 °C (ref. [15a]). Reaction with pyrrole: 69% yield and 87% *ee* with 5 mol% catalyst at -40 °C (ref. [16]).

[18] For comparison, a DNA-based copper(II) catalyst (30 mol%) provided for the same malonodinitrile Michael addition product with an enantioselectivity of 36% *ee* at 4 °C, see: Y. Li, C. Wang, G. Jia, S. Lu, C. Li, *Tetrahedron* **2013**, *69*, 6585 – 6590.

[19] For reviews on the asymmetric construction of all-carbon quaternary stereocenters, see: a) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363 – 5367; b) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473 – 1482; c) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369 – 396; d) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583 – 1614; e) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295 – 7306; f) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593 – 4623; g) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247 – 7290; h) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181 – 191.

[20] For comparison, a bis(oxazolinyl)pyridine-cerium(IV) triflate catalyst provided for the same nitrone cycloaddition reaction 99% yield with 97% *ee* and $>$99:1 *endo*/*exo* with 5 mol% catalyst at 0 °C, see: D. A. Evans, H.-J. Song, K. R. Fandrick, *Org. Lett.* **2006**, *8*, 3351 – 3354.

[21] For related Lewis acid catalyzed asymmetric 1,3-dipolar cycloadditions, see: a) K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1994**, *59*, 5687 – 5691; b) K. V. Gothelf, I. Thomsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **1996**, *118*, 59 – 64; c) S. Kobayashi, M. Kawamura, *J. Am. Chem. Soc.* **1998**, *120*, 5840 – 5841; d) S. Kanemasa, Y. Oderaotoshi, J. Tanaka, E. Wada, *J. Am. Chem. Soc.* **1998**, *120*, 12355 – 12356; e) C. Palomo, M. Oiarbide, E. Arceo, J. M. García, R. López, A. González, A. Linden, *Angew. Chem. Int. Ed.* **2005**, *44*, 6187 – 6190; *Angew. Chem.* **2005**, *117*, 6343 – 6346; f) M. P. Sibi, Z. Ma, K. Itoh, N. Prabagaran, C. P. Jasperse, *Org. Lett.* **2005**, *7*, 2349 – 2352; g) K. Phomkeona, T. Takemoto, Y. Ishima, K. Shibatomi, S. Iwasa, H. Nishiyama, *Tetrahedron* **2008**, *64*, 1813 – 1822; h) S. Barroso, G. Blay, M. C. Muñoz, J. R. Pedro, *Org. Lett.* **2011**, *13*, 402 – 405; i) D. Chen, Z. Wang, J. Li, Z. Yang, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 5226 – 5229.

[22] For a review on hetero-Diels – Alder reactions of ketones, see: K. A. Jørgensen, *Eur. J. Org. Chem.* **2004**, 2093 – 2102.

[23] For related Lewis acid catalyzed asymmetric hetero-Diels–Alder reactions, see: a) J. Thorhauge, M. Johannsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **1998**, *37*, 2404 – 2406; *Angew. Chem.* **1998**, *110*, 2543 – 2546; b) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635 – 1649; c) H. Audrain, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 4487 – 4497; d) Y. Shin, C.-E. Yeom, M. Kim, B. Kim, *Synlett* **2008**, 89 – 93; e) Y. Zhu, M. Xie, S. Dong, X. Zhao, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 8202 – 8208; f) Y. Zhou, Y. Zhu, L. Lin, Y. Zhang, J. Zheng, X. Liu, X. Feng, *Chem. Eur. J.* **2014**, *20*, 16753 – 16758.

[24] For related Lewis acid catalyzed asymmetric Diels-Alder reactions, see: a) E. J. Corey, N. Imai, H. Y. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 728 – 729; b) D. A. Evans, S. J. Miller, T. Lectka, *J. Am. Chem. Soc.* **1993**, *115*, 6460 – 6461; c) K. V. Gothelf, K. A. Jorgensen, *J. Org. Chem.* **1995**, *60*, 6847 – 6851; d) D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross, S. J. Miller, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798 – 800; *Angew. Chem.* **1995**, *107*, 864 – 867; e) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron Lett.* **1996**, *37*, 3815 – 3818; f) I. Sagasser, G. Helmchen, *Tetrahedron Lett.* **1998**, *39*, 261 – 264; g) S. Otto, G. Boccaletti, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **1998**, *120*, 4238 – 4239; h) D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 7582 – 7594; i) M. P. Sibi, L. M. Stanley, X. Nie, L. Venkatraman, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **2007**, *129*, 395 – 405; j) A. J. Boersma, J. E. Klijn, B. L. Feringa, G. Roelfes, *J. Am. Chem. Soc.* **2008**, *130*, 11783 – 11790; k) C. Wang, G. Jia, J. Zhou, Y. Li, Y. Liu, S. Lu, C. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 9352 – 9355; *Angew. Chem.* **2012**, *124*, 9486 – 9489; l) A. J. Boersma, B. de Bruin, B. L. Feringa, G. Roelfes, *Chem. Commun.* **2012**, *48*, 2394 – 2396.

[25] For the conjugate addition to α,β-unsaturated 2-acyl benzimidazoles, see: M. Yoshida, H. Ohmiya, M. Sawamura, *J. Am. Chem. Soc.* **2012**, *134*, 11896 – 11899. See also ref. [15b].

[26] For the conjugate addition to α,β-unsaturated 2-acyl thiazoles, see: a) A. Dondoni, L. Kniezo, M. Martinkova, *J. Chem. Soc. Chem. Commun* **1994**, 1963 – 1964; b) A. Dondoni, A. Marra, A. Boscarato, *Chem. Eur. J.* **1999**, *5*, 3562 – 3572; c) M. Sani, G. Fossati, F. Huguenot, M. Zanda, *Angew. Chem. Int. Ed.* **2007**, *46*, 3526 – 3529; *Angew. Chem.* **2007**, *119*, 3596 – 3599; d) P. S. Shankar, M. Sani, G. Terraneo, M. Zanda, *Synlett*

2009, 1341 – 1345; e) P. Kwiatkowski, A. Cholewiak, A. Kasztelan, *Org. Lett.* **2014**, *16*, 5930 – 5933. See also ref. [15b].

[27] For the conjugate addition to α,β-unsaturated 2-acyl pyridines, see: a) M. P. Sibi, Y. H. Yang, *Synlett* **2008**, 83 – 88; b) P. K. Singh, V. K. Singh, *Org. Lett.* **2008**, *10*, 4121 – 4124; c) N. Molleti, N. K. Rana, V. K. Singh, *Org. Lett.* **2012**, *14*, 4322 – 4325; d) S. Lin, Y. Wei, F. Liang, *Chem. Commun.* **2012**, *48*, 9879 – 9881; e) G. Blay, C. Incerti, M. C. Muñoz, J. R. Pedro, *Eur. J. Org. Chem.* **2013**, 1696 – 1705; f) X.-Q. Hao, J.-J. Huang, T. Wang, J. Lv, J.-F. Gong, M.-P. Song, *J. Org. Chem.* **2014**, *79*, 9512 – 9530.

[28] For the conjugate addition to α,β-unsaturated *N*-acyl oxazolidinones, see: a) S. Kobayashi, C. Ogawa, M. Kawamura, M. Sugiura, *Synlett* **2001**, 0983 – 0985; b) D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, *124*, 2134 – 2136; c) A. W. Hird, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2003**, *42*, 1276 – 1279; *Angew. Chem.* **2003**, *115*, 1314 – 1317; d) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4032 – 4035; *Angew. Chem.* **2005**, *117*, 4100 – 4103; e) C. Palomo, R. Pazos, M. Oiarbide, J. M. García, *Adv. Synth. Catal.* **2006**, *348*, 1161 – 1164; f) A. M. M. Abe, S. J. K. Sauerland, A. M. P. Koskinen, *J. Org. Chem.* **2007**, *72*, 5411 – 5413; g) L. Fadini, A. Togni, *Tetrahedron: Asymmetry* **2008**, *19*, 2555 – 2562; h) M. P. Sibi, Y.-H. Yang, S. Lee, *Org. Lett.* **2008**, *10*, 5349 – 5352; i) Y. Liu, B. Sun, B. Wang, M. Wakem, L. Deng, *J. Am. Chem. Soc.* **2009**, *131*, 418 – 419; j) S. Murarka, I. Deb, C. Zhang, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 13226 – 13227; k) Y. Huang, E. Tokunaga, S. Suzuki, M. Shiro, N. Shibata, *Org. Lett.* **2010**, *12*, 1136 – 1138; l) S. Harada, T. Morikawa, A. Nishida, *Org. Lett.* **2013**, *15*, 5314 – 5317; m) L. Wen, L. Yin, Q. Shen, L. Lu, *Acs Catal.* **2013**, *3*, 502 – 506; n) Y. Sakaguchi, N. Kurono, K. Yamauchi, T. Ohkuma, *Org. Lett.* **2014**, *16*, 808 – 811. See also ref. [15b].

[29] For the conjugate addition to α,β-unsaturated *N*-acylthiazolidinethiones, see: D. A. Evans, R. J. Thomson, F. Franco, *J. Am. Chem. Soc.* **2005**, *127*, 10816 – 10817. See also ref. [15b].

[30] For conjugate additions with α,β-unsaturated *N*-acyl pyrazoles, see: a) C. Kashima, K. Takahashi, I. Fukuchi, K. Fukusaka, *Heterocycles* **1997**, *44*, 289 – 304; b) M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **1998**, *120*, 6615 – 6616; c) C. Kashima, K. Fukusaka, K. Takahashi, Y. Yokoyama, *J. Org. Chem.* **1999**, *64*, 1108 – 1114; d) K. Itoh, S. Kanemasa, *J. Am. Chem. Soc.* **2002**, *124*, 13394 – 13395; e) C. Kashima, Y. Miwa, S. Shibata, H. Nakazono, *J. Heterocycl. Chem.* **2003**, *40*, 681 – 688; f) K. Itoh, Y. Oderaotoshi, S. Kanemasa, *Tetrahedron: Asymmetry* **2003**, *14*, 635 – 639; g) K. Itoh, M. Hasegawa, J. Tanaka, S. Kanemasa, *Org. Lett.* **2005**, *7*, 979 – 981; h) H. Yanagita, K. Kodama, S. Kanemasa, *Tetrahedron Lett.* **2006**, *47*, 9353 – 9357; i) K. Ishihara, M. Fushimi, *Org. Lett.* **2006**, *8*, 1921 – 1924; j) M. P. Sibi, K. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 8064 – 8065; k) F. Ono, M. Hasegawa, S. Kanemasa, J. Tanaka, *Tetrahedron Lett.* **2008**, *49*, 5105 – 5107; l) M. Hasegawa, F. Ono, S. Kanemasa, *Tetrahedron Lett.* **2008**, *49*, 5220 – 5223; m) X.-Q. Dong, X. Fang, H.-Y. Tao, X. Zhou, C.-J. Wang, *Chem. Commun.* **2012**, *48*, 7238; n) X.-Q. Dong, X. Fang, H.-Y. Tao, X. Zhou, C.-J. Wang, *Adv. Synth. Catal.* **2012**, *354*, 1141 – 1147; o) J. Zhang, X. Liu, R. Wang, *Chem. Eur. J.* **2014**, *20*, 4911 – 4915. See also ref. [15b].

[31] For the conjugate addition to α,β-unsaturated acyl phosphonates, see: a) H. Jiang, M. W. Paixão, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 2775 – 2783; b) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10780 – 10781; c) Y. K. Kang, K. H. Suh, D. Y. Kim, *Synlett* **2011**, 1125 – 1128; d) N. Takenaka, J. P. Abell, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 742 – 743; e) P. Bachu, T. Akiyama, *Chem. Commun.* **2010**, *46*, 4112 – 4114. See also ref. [15b].

[32] For the conjugate addition to α,β-unsaturated ketoesters, see, for example: a) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 160 – 163; *Angew. Chem.* **2001**, *113*, 164 – 167; b) K. A. Jørgensen, *Synthesis* **2003**, 1117 – 1125; c) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem. Int. Ed.* **2008**, *47*, 593 – 596; *Angew. Chem.* **2008**, *120*, 603 – 606; d) S.-L. Zhao, C.-W. Zheng, H.-F. Wang, G. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 2811 – 2816; e) Y. Liu, D. Shang, X. Zhou, Y. Zhu, L. Lin, X. Liu, X. Feng, *Org. Lett.* **2010**, *12*, 180 – 183; f) J. Lv, X. Li, L. Zhong, S. Luo, J.-P. Cheng, *Org. Lett.* **2010**, *12*, 1096 – 1099; g) L. Zhou, L. Lin, W. Wang, J. Ji, X. Liu, X. Feng, *Chem. Commun.* **2010**, *46*, 3601 – 3603; h) B. Yang, F. Xie, H. Yu, K. Shen, Z. Ma, W. Zhang, *Tetrahedron* **2011**, *67*, 6197 – 6201; i) J. Lv, L. Zhang, Y. Zhou, Z. Nie, S. Luo, J.-P. Cheng, *Angew. Chem. Int. Ed.* **2011**, *50*, 6610 – 6614; *Angew. Chem.* **2011**, *123*, 6740 – 6744; j) L. Gremaud, A. Alexakis, *Angew. Chem. Int. Ed.* **2012**, *51*, 794 – 797; *Angew. Chem.* **2012**, *124*, 818 – 821; k) L. Liu, H. Ma, Y. Xiao, F. Du, Z. Qin, N. Li, B. Fu, *Chem. Commun.* **2012**, *48*, 9281 – 9283; l) J. Duan, F. Cao, X. Wang, C. Ma, *Chem. Commun.* **2013**, *49*, 1124 – 1126; m) Y. Zhang, X. Liu, X. Zhao, J. Zhang, L. Zhou, L. Lin, X. Feng, *Chem. Commun.* **2013**, *49*, 11311 – 11313; n) H.-G. Cheng, L.-Q. Lu, T. Wang, Q.-Q. Yang, X.-P. Liu, Y. Li, Q.-H. Deng, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 3250 – 3254; *Angew. Chem.* **2013**, *125*, 3332 – 3336; o) S. Zhang, K. Xu, F. Guo, Y. Hu, Z. Zha, Z. Wang, *Chem. Eur. J.* **2014**, *20*, 979 – 982; p) Q. Wang, J. Gong, Y. Liu, Y. Wang, Z. Zhou, *Tetrahedron* **2014**, *70*, 8168 – 8173; q) S.-J. Jia, D.-M. Du, *Tetrahedron: Asymmetry* **2014**, *25*, 980 – 988; r) J. Wang, B. Wang, P. Cao, J. Liao, *Tetrahedron Lett.* **2014**, *55*, 3450 – 3453; s) E. Sánchez-Larios, K. Thai, F. Bilodeau, M. Gravel, *Org. Lett.* **2011**, *13*, 4942 – 4945; t) A. Lefranc, L. Gremaud, A. Alexakis, *Org. Lett.* **2014**, *16*, 5242 – 5245; u) J. Wang, M. Wang, P. Cao, L. Jiang, G. Chen, J. Liao, *Angew. Chem. Int. Ed.* **2014**, *53*, 6673 – 6677; *Angew. Chem.* **2014**, *126*, 6791 – 6795; v) Y. Zhang, N. Yang, X. Liu, J. Guo, X. Zhang, L. Lin, C. Hu, X. Feng, *Chem. Commun.* **2015**, *51*, 8432 – 8435.

[33] For conjugate additions to α,β-unsaturated Weinreb amides, see: a) R. Shintani, T. Kimura, T. Hayashi, *Chem. Commun.* **2005**, 3213 – 3214; b) J. R. de Alaniz, M. S. Kerr, J. L. Moore, T. Rovis, *J. Org. Chem.* **2008**, *73*, 2033 – 2040; c) L. Li, J.-Y. Guo, X.-G. Liu, S. Chen, Y. Wang, B. Tan, X.-Y. Liu, *Org. Lett.* **2014**, *16*, 6032 – 6035.

[34] 2-Acyl imidazoles can be converted to a wide variety of carbonyl compounds. See ref. [15b] and also: a) S. Ohta, S. Hayakawa, K. Nishimura, M. Okamoto, *Chem. Pharm. Bull.* **1987**, *35*, 1058 – 1069; b) A. Miyashita, Y. Suzuki, I. Nagasaki, C. Ishiguro, K. Iwamoto, T. Higashino, *Chem. Pharm. Bull.* **1997**, *45*, 1254 – 1258.

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